Massoud Mahmoudi *Editor*

Challenging Cases in Pulmonology

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To the memory of my father, Mohammad H. Mahmoudi, and to my mother, Zohreh, my wife, Lily, and my sons Sam and Sina for their continuous support and encouragement.

Preface

It is my pleasure to present to you the *Challenging Cases in Pulmonology*. This book like our two preceding titles, *Challenging Cases in Allergy and Immunology* (2009) and *Challenging Cases in Allergic and Immunologic Diseases of the Skin* (2010), presents the topic in a case-based study format.

Pulmonology is a fascinating discipline of medicine that overlaps with other specialties such as allergy and immunology and infectious diseases among others. This area of medicine includes diagnosis and treatment of respiratory diseases and ailments that have affected the respiratory system. Approaching a patient with pulmonary disorder has always been challenging partly due to the fact that at times the patient is either a poor historian or presents in late stages of the respiratory complication.

I have been fortunate to use the help and expertise of over 30 authorities in the fields of allergy/immunology, pulmonology, and infectious diseases to form this collection of challenging cases. This book is intended to target educators and clinician in the field of pulmonology, allergy/immunology, and infectious diseases, fellows-in-training, residents in pediatrics and internal medicine, primary care physicians, nurse practitioners, medical and nursing students, and allied health providers.

This book consists of 7 parts and 16 chapters and each chapter presents 2–3 cases. Our unique style of these series is comprised of a short abstract followed by case presentation, working diagnosis, data, final diagnosis, and discussion. In addition, to stimulate the reader's thought process, we have added 5–10 multiple choice questions and answers.

This book is a combined effort of all contributors with the help and support of the Springer publisher. I would like to express my thanks to Richard Lancing, the executive editor who has supported this and the previous two titles; Andy Kwan, editorial assistant; Ms. Maureen Pierce the developmental editor; and the entire editorial and publishing staff at Springer.

We have received several favorable reviews for the previous titles and we hope the readers also find this collection a valuable and helpful resource. I will be happy to hear your comments and use them in future editions of this book. I can be reached at allergycure@sbcglobal.net.

Massoud Mahmoudi

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Part I
Allergic and Immunologic Diseases of the Lung

Chapter 1
Allergic Asthma

Thomas L. Mertz and Timothy J. Craig

Abstract Allergic asthma, also known as atopic asthma, is one type of extrinsic asthma that is characterized by an exaggerated immune response to a variety of indoor and outdoor allergens. The most commonly associated indoor allergens are house dust mites, cockroaches, and animals such as cats. However, outdoor allergens such as alternaria mold, ragweed, tree, and grass pollen are also known triggers. The relationship between asthma and allergy is very complex, and atopic individuals seem to be at increased risk for asthma [1]. The clinical presentation of asthma can vary greatly and depends on the stage and severity of the underlying disease process. The development of allergic asthma is dependent on the T-Helper two (TH_2) predominant immune response. The diagnosis of allergic asthma must be made clinically with consistent history and observed worsening of the condition following exposure to a suspected allergen. Diagnostic testing, in general, is often not needed to make the diagnosis if the history is compelling. Pulmonary function testing (PFT) reveals the classic obstructive pattern of asthma with observed reversibility following administration of $beta_2$ agonists. Specific sensitivity to suspected allergens can be ascertained by interpretation of skin prick testing or serum specific IgE levels. Treatment involves removing, if possible, the inciting allergens. Other treatments involve ones typically utilized in any asthmatic such as inhaled corticosteroids and $beta_2$ agonists. In some patients airway remodeling can occur if the inflammatory response is left unchecked; therefore, controlling the underlying inflammation is imperative.

Keywords Aeroallergen • Allergy • Asthma • Atopy

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Case 1

A 17-year-old male, with history of asthma, atopic dermatitis, and hay fever, presented to a clinic for further evaluation and treatment. He was accompanied by his father who reported that his son had problems with asthma "since infancy," and had not been in good control. Multiple asthma triggers included upper respiratory infection, exercise, strong odors, cold weather, and allergens. The patient reported having year round problems with sneezing and nasal pruritis as well as difficulties with ocular injection and erythema. Increasing symptoms of cough, wheezing, and dyspnea had recently necessitated the use of a rescue inhaler up to four to five times daily. His maintenance medications consisted of combination long acting beta agonist (LABA)/inhaled corticosteroid, leukotriene antagonist, and for the last month, prednisone 20 mg daily. Despite his compliance with his other medicines, he was not able to taper off the prednisone.

The patient lived with his parents and a 14-year-old sister. He reported there was a strong family history of asthma. He also reported that they did not have pets, but his parents did smoke in the home. They lived in an "older" home that did not have an insect infestation problem, but had mold in the basement. His immunizations, including influenza and pneumococcal, were up-to-date.

On physical exam, his pulse oximetry was 95% on room air. Although he was in no obvious respiratory distress, he had overt bilateral expiratory wheezes heard on auscultation. He did not have accessory muscle use. Pulmonary function testing performed in the office revealed his FVC was 70% of predicted, FEV1 31% of predicted, FEV1/FVC ratio of 0.55 and FEF 25/75 was 13% of predicted, which was consistent with a severe obstructive pattern. He had a history of significant improvement after albuterol on PFT in the past. Skin testing to aeroallergens was done in the past. His father reported that his son tested positive to so many different allergens that the allergist had to wipe off the extract on his skin and stop the testing. The patient was unable to undergo repeat testing at his current evaluation secondary to his respiratory status. Previous workup revealed a normal echocardiogram as well as a normal CBC, with the exception of an elevated eosinophil percentage of 13% (0–6), absolute count 700 (<350). Previous chest radiograph revealed nonspecific modest prominence of central peribronchial markings. Please see Fig. 1.1. This reveals modest prominence of central peribronchial markings. This is a nonspecific finding, associated with inflammatory and allergic processes.

With the Presented Data What Is Your Working Diagnosis?

Because of his history of poorly controlled asthma despite compliance with adequate treatment, other factors were likely contributing to this overall clinical picture. Allergic sensitization was playing a role in this atopic patient's severe asthma. The diagnosis of α-1 antitrypsin deficiency was suspected given his long history of secondhand smoke exposure. A diagnosis of allergic bronchopulmonary aspergillosis (ABPA) was also entertained given his elevated eosinophil percentage.

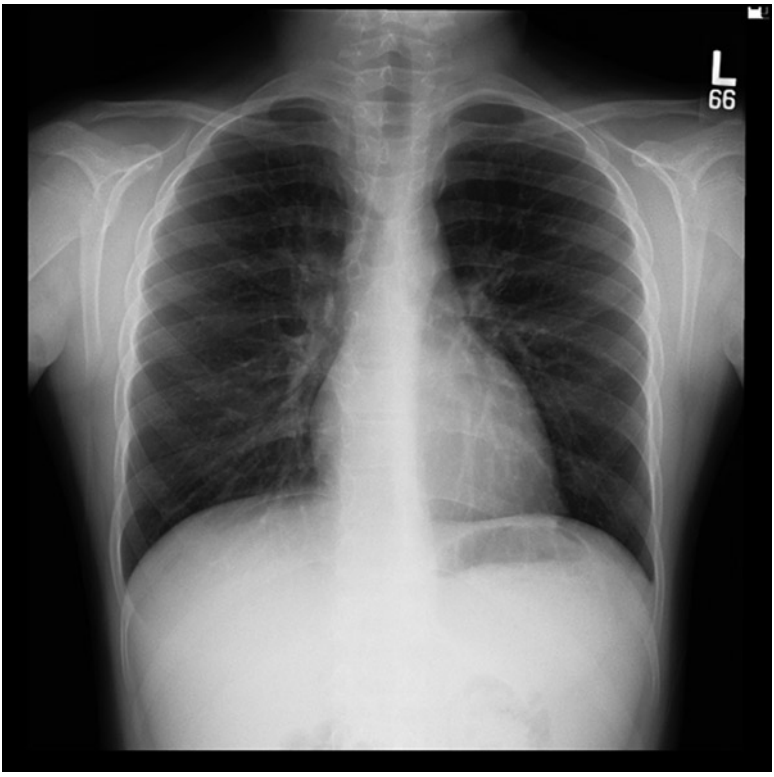

Fig. 1.1 Chest X-ray from Case 1: CXR reveals modest prominence of central peribronchial markings. This is a nonspecific finding, associated with inflammatory and allergic processes

Other conditions on the differential included: congestive heart failure, cystic fibrosis, pulmonary embolism, and mechanical obstruction of the upper airways; however, most seemed unlikely given his past medical, family history and former workup.

Additional History and Workup

Peribronchial Cuffing

This occurs when excess fluid or mucus builds up in the small airway passages of the lung.

The patient underwent serum specific IgE levels to aeroallergens, which revealed that he was positive to dust mites, timothy grass, alternaria, oak pollen, maple pollen, cockroaches and ragweed. His total IgE level was elevated at 606 (0–100). Additionally, his alpha-1 antitrypsin level was normal at 130 (83–199)

(continued)

Peribronchial Cuffing (continued)

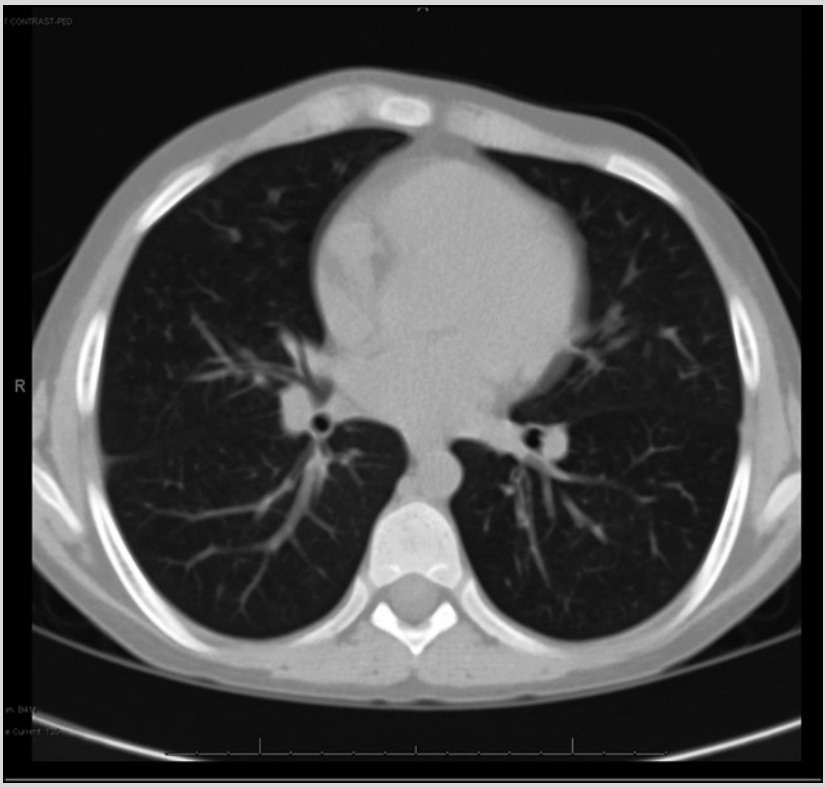

Fig. 1.2 Chest CT from Case 1: Peribronchial cuffing. This occurs when excess fluid or mucus builds up in the small airway passages of the lung

and his genotype was MM which is the normal allele. He had negative *Aspergillus precipitin* and *Aspergillus fumigatus* antibody. Because of the disease severity a CT scan of the chest was performed, which demonstrated ground-glass opacities consistent with atelectasis with pronounced central peribronchial cuffing. There was no evidence of bronchiectasis or pulmonary embolism. Please see Fig. 1.2.

What Is Your Diagnosis and Why?

The patient was diagnosed with severe allergic or atopic asthma. The remainder of his workup failed to reveal other potential causes for this constellation of symptoms and he did not meet the criteria for the diagnosis of ABPA. The diagnosis of atopic

asthma was supported by multiple elevated serum specific IgE levels to aeroallergens, elevated total serum IgE level, findings on imaging, PFT, and his clinical presentation. He was treated with omalizumab subcutaneously every 4 weeks and improved dramatically. Eventually, he was able to taper his use of the oral prednisone and showed improvements both in his symptoms and in his PFT. The primary use of omalizumab is for patients such as this with severe, persistent, allergic asthma who remain uncontrolled despite high doses of corticosteroids.

Case 2

A 10-year-old female was referred for evaluation of severe persistent asthma. She had a history of allergic rhinitis, atopic dermatitis, and cold induced urticaria. Diagnosed with asthma when she was only a few months old, she reported that with each subsequent year her asthma worsened, requiring multiple hospitalizations throughout her lifetime for asthma exacerbations. In the last year alone, she reported being hospitalized on three different occasions. Triggers included exertion, exposure to cold air, and upper respiratory infections. On a bad day, which happened about three to four times per week, she reported using her albuterol as frequently as every 2 h. She denied having fever, chills, productive cough, or recurrent infections, but did admit to having recurrent heartburn, which was stabilized by taking omeprazole. She also reported having frequent school absenteeism because of breathing difficulty. She lived in a remodeled farm house with her mother, father, sister, brother and two pet dogs. The house used oil heat and a wood stove was used intermittently. The family followed environmental avoidance measures and used allergen coverings for her bedding and attempted to vacuum the house regularly. There were no problems with insects or mold and no one smoked in the home. There was a family history of asthma.

On physical exam, she had normal breath sounds and the only significant finding was nasal congestion and cobble stoning of her oropharynx. At that time, she was prescribed a LABA/inhaled corticosteroid combination, montelukast and tiotroprium bromide. She required frequent courses of oral steroids, typically about once every 8 weeks. During her hospitalizations, she had chest x-rays performed which revealed hyperinflation and nonspecific peribronchial thickening. She also had an upper airway endoscopy that was normal without gross or biopsy evidence of reflux esophagitis. She was evaluated previously by an allergist, and her mother reported that she was positive to most of the things that were tested. Immunotherapy was attempted, but was discontinued secondary to recurrent problems with asthma exacerbations. The patient's PFT are shown below. Please see Fig. 1.3.

With the Presented Data What Is Your Working Diagnosis?

The patient had very poorly controlled asthma, and given her history, her asthma would be classified as severe persistent. Her PFT, however, revealed only a mildly

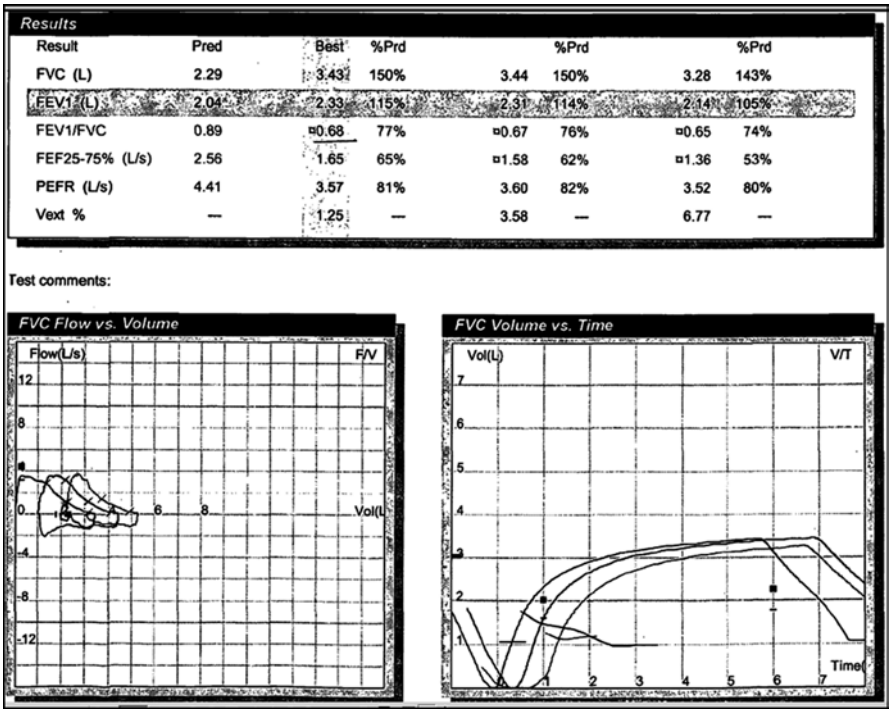

Fig. 1.3 PFT from Case 2: What is your interpretation?

obstructive pattern. Because of the patient's history of allergic sensitization to aeroallergens and other atopic diseases such as urticaria, atopy is a definite consideration that could be contributing to her severe asthma. Another consideration is alpha 1-antitrypsin, but this is less likely given her age. Other possible etiologies include cystic fibrosis, pneumonia, other upper respiratory infections, hypersensitivity pneumonitis, ABPA or vocal cord dysfunction.

Additional History and Workup

The patient had a CT scan of the chest which was without abnormality and there was no sign of bronchiectasis. The CBC with differential was reassuring except for an elevated eosinophil count of 1,080 (0–700). Her total serum IgE was elevated 1,123 (0–100), and serum specific IgE was elevated to dust mite, cat and alternaria. Her dog's IgE level was especially high at 80 kU/L (<0.35). The remainder of the aeroallergen testing was negative, which included aspergillus IgE level. In addition, an IgG antibody against aspergillus was negative. Her sweat test was normal.

Alpha-1 antitrypsin phenotype was normal (MM), and her level was 158 (83–199) which was also in the normal range.

What Is Your Diagnosis and Why?

Her results were indicative of a significantly atopic state with elevated serum specific to only a select number of the indoor aeroallergens; outdoor allergens were negative. Of note, her anti-dog IgE level is not only positive, but it was also quite high, supporting the idea that ongoing exposure to dog in the home is driving her asthmatic inflammation and lack of control. Given the lack of other etiology being found, dog exposure was the suspected trigger. This was later confirmed when she had improvement of her symptoms and less need for medicines once the dogs were removed from the home and environmental avoidance measures were instituted.

Discussion

Asthma is a clinical syndrome that typically consists of three findings:

1. Recurrent episodes of airway obstruction.
2. Airway hyper-responsiveness.
3. Inflammatory changes in the airways and, in some cases, remodeling.

Atopy, defined by Middleton, "is the tendency to mount IgE antibody response to environment proteins" [1]. Numerous studies have reported the strong association between atopy and asthma. There seems to be complex interactions between environment, economic status, location of residence, genetics, as well as other factors that contribute to the overall clinical picture in each individual patient with asthma. Regardless of underlying diagnosis, atopic children have a strong association with attacks of wheezing and dyspnea [1]. Research has demonstrated a high incidence of aeroallergen sensitivity in children with asthma. Eosinophilia and total serum IgE have a robust positive correlation to aeroallergen sensitization [2]. Historically, indoor allergens are thought to most likely trigger asthma, but Ogershok et al. performed a study of children with asthma, ages 6 months to 10 years, and they found that nearly 40% of 1–3-year-old children with asthma were found to have sensitivity to outdoor allergens, as well [3]. Asthmatic patients who participated in the Asthma Clinical Research Network (ACRN) were found to have differences in the likelihood of having positive skin prick testing to environmental allergens based on when in life they developed asthma. Ninety-six percent of patients with the onset of asthma before 30 years of age were found to have sensitization to aeroallergens. Alternatively, patients with later onset of asthma had an 88% likelihood of having positive skin prick testing [2].

Epidemiology

Worldwide atopic diseases have been increasing in prevalence, and asthma is no exception. The highest incidence is found in more industrialized western countries [4]. Several different hypotheses have tried to explain the overall increase, but the exact etiology remains unknown. Asthma can present at any age, but the peak age is 3 years. In childhood, males are more likely to be asthmatic. After age 20 this equalizes between the genders, and after age 40 it is more common in females [5]. In the United States, asthma is one of the most common reasons to seek medical treatment, representing an enormous cost to society. Yearly direct and indirect costs of asthma care have been in the billions.

Clinical Signs and Symptoms

The clinical presentation of asthma can vary greatly and depends on the stage and severity of the underlying disease process. Asthma has a spectrum of presentation from chronically coughing to an acute severe episode of respiratory distress necessitating intubation. The most common sign and symptoms are wheezing and dyspnea, respectively. For example, for patients previously sensitized to an aeroallergen, re-exposure to this particular antigen may exacerbate their asthma. In many cases an inciting trigger can be elicited, but at times a patient may have an acute attack of asthma without a known trigger or exposure. During the physical exam, patients may be tachypneic or tachycardic and may be using accessory respiratory muscles or having paradoxical abdominal movement to generate an adequate tidal volume. Wheezing can be heard on auscultation, but the absence of wheezing is not always an encouraging sign. In fact, it may be demonstrative of more ominous obstruction and impending respiratory failure. Pulse oximetry typically can be above 90%, even in severe attacks, and in most cases, is not a reliable sign to use independently. In cases of severe asthma pulsus paradoxus (which is an exaggerated decrease in the systolic pressure during inspiration) may be seen and mental status changes can occur if the patient is becoming hypercapnic or having severe hypoxia.

Pathophysiology

Genetics

Asthma has been shown to be more common in first-degree relatives of patients with asthma and it has classically been shown to be more prevalent in monozygotic versus dizygotic twins [6]. Several genes have been linked to different phenotypes of asthma and it appears to be polygenetic in nature rather than having one single

Table 1.1 Allergens that have immunomodulation activity

Allergen	Proposed mechanism	Effect
Pollen	Increase NADPH oxidase	Increase airway inflammation
Dermatophagoides Pteronyssinus	Mimic LPS cofactor of TLR-4	Promotes TH_2 response
Dermatophagoides Pteronyssinus, farinae Cockroach Fungi	Up regulate chitinase	Increase chemokine production
Cat Dermatophagoides Ragweed	Stimulation of dendritic cells	IgE class switching

Adapted from [6]

dominant gene involved in its pathogenesis. Genes that have been found to contribute to the pathogenesis of asthma include ADAM33, DPP10, PHF11, GPRA, TIM-1, PDe4D, OPN3, and ORMDL3 [7]. Different ethnic groups have different incidence and severity of asthma, a finding that should be taken into consideration when genetic evaluation is considered [7].

Pathology

Allergic asthma is a type 1 hypersensitivity reaction and is the result of an exaggerated inflammatory process that is thought to be caused by a multifaceted interaction between the environment and the immune system in genetically predisposed individuals. Allergens vary on their ability to elicit an immune response (see Table 1.1). Dust mites, cats and ragweed allergens can directly activate dendritic cells in the airway. Others such as cockroaches, fungi and dust mites contain chitin which causes direct release of chemokines. Pollens inherently contain NADPH oxidase which increases inflammation by increasing reactive oxygen species. Certain dust mite allergens can directly stimulate an increased TH_2 response on their own [6].

Allergens are first taken up by dendritic cells in the respiratory mucosa. These cells then present the antigen to antigen specific TH_2 cells. TH_2 driven inflammation that favors IgE production is the hallmark of allergic asthma [6]. These TH_2 cells release cytokines such as IL-4, IL-5, IL-9 and IL-13 that further potentiate allergic inflammation. Locally released chemokines recruit other inflammatory cells such as eosinophils, macrophages, neutrophils and more T-Cells. T-cells then induce class switching of B-cells to make IgE rather than IgM. The IgE then binds to the FceR1 receptors on mast cells and basophils. With subsequent exposure to an allergen, IgE, which is bound to the FceR1 receptor, binds the antigen and can induce cross-linking of the IgE. This cross-linking precipitates a massive release of inflammatory mediators such

as leukotrienes, prostaglandins and histamine and the production of cytokines. The result of this mediator release is airway smooth muscle contraction, increased edema, increased mucus secretion and chemotaxis of inflammatory cells [6].

Workup

Laboratory Evaluation

Laboratory evaluation for asthma is not typically necessary or very helpful. During acute asthma attacks, an arterial blood gas may be helpful in staging the severity of attack, if the clinical picture is otherwise somewhat unclear. Obtaining a complete blood cell count may be helpful to look for signs of leukocytosis with left shift, if the possibility of concurrent infectious process is suspected. In allergic asthma, a total serum IgE level can be helpful to further refute or support the notion that allergy may be contributing to the problem or if omalizumab is indicated. In addition, serum specific IgE levels to environmental allergens can be obtained at times when skin prick testing is impractical or contraindicated allowing aeroallergen triggers to be identified.

Radiographic Evaluation

Chest radiograph may show evidence of hyperinflation, but is typically normal. During an acute attack, plain films of the chest may be needed to rule out any infectious process that could be contributing to the overall clinical picture or complications of asthma such as pneumothorax or atelectasis. Patients should undergo a baseline chest x-ray if a new diagnosis of asthma is being entertained to rule out anatomical abnormalities and other diagnoses that can mimic asthma.

Pulmonary Function Testing

Pulmonary function testing (PFT) is one the most helpful and most commonly utilized tests to initially diagnose asthma. A serial evaluation can be performed to follow the current status of the disease and to monitor the response to therapy. PFTs are especially helpful during acute attacks to determine the change from the patient's baseline. Asthma has an obstructive pattern on PFTs, which usually is demonstrated by a low FEV_1 (Forced Expiratory Volume in 1 s) and a ratio of FEV_1/FVC ratio of <80%. Diffusion capacity (DLCO) is typically normal in asthma, in contrast with other obstructive diseases like chronic obstructive pulmonary disease (COPD) where it is often reduced. Asthma is usually an airway obstructive disorder that can be reversed or partially reversed with a bronchodilator such as albuterol. A diagnostic reversal is a >12% increase and 200 ml increase in the FEV_1 [8].

Peak Flow Testing

Peak flows are not a replacement for spirometry, but when used serially can help determine changes in asthma stability. During hospitalization and Emergency Department (ED) visits, serial assessment can gauge improvement, predict response to therapy, and help triage to higher and lower levels of care. In a study in an ED setting, when combined with uninterrupted pulse oximetry monitoring, peak expiratory flow rate measured after 15–60 min of treatment was found to be a good prognostic indicator of response [9]. If treatment did not positively impact subsequent peak flow measurements, a more complicated course with subsequent hospitalization was more likely [9]. For patients with disparity between symptoms and FEV_1, peak flows can also be used to alter therapy based upon an asthma action plan.

Sputum Findings

The sputum of a patient with asthma may be either clear or slightly colored. It typically contains eosinophils, Charcot-Leyden crystals (lysophospholipase, which is a breakdown product of eosinophils), Curschmann's spiral (mucus plugs), or Creola bodies (ciliated columnar cells sloughed from the bronchial mucosa).

Fractional Exhaled Nitric Oxide (FeNO)

Nitric oxide is a gas that is released into the airway during an inflammatory response. FeNO is an indirect, noninvasive marker of eosinophilic, airway inflammation. Patients with asthma have higher levels of FeNO than their nonasthmatic cohorts. FeNO is typically not elevated in COPD; therefore, this is another way, although with multiple limitations, to distinguish between obstructive lung conditions. The normal range for FeNO is 0–20 parts per billion. Levels tend to be higher in atopic individuals [2].

Bronchial Challenge Test

Increasing concentrations of methacholine, a drug that can induce bronchoconstriction, is given to patients in a controlled setting to detect the presence of airway hyper-responsiveness in patients thought to have asthma. This is a helpful aid in the differential diagnosis or for research to determine efficacy of anti-inflammatory therapy. Patients with asthma have hyper-reactive airways and react to lower doses of methacholine than do patients without asthma. Positive methacholine challenge is defined as the dose of methacholine that causes a fall in FEV_1 of 20% (PC_{20}) or

more [2]. An alternative agent that has just been approved for use in the USA is mannitol. Other challenge tests include specific allergen, exercise, histamine, eucapnic hyperventilation and hypertonic saline.

Specific Allergen Investigation

The inciting allergen can be identified by performing further diagnostic testing. Skin prick testing can help identify specifically which antigen a patient may be hypersensitive to. If skin testing cannot be performed secondary to active asthma, low FEV_1, severe eczema, recent ingestion of antihistamines or dermatographia, in vitro serum specific IgE levels to a particular allergen can be measured. Skin prick testing and in vitro specific IgE closely correspond with airway hyperresponsiveness, and both have about equal sensitivity and specificity, with skin tests having lower cost per unit [2].

Management, Treatment and Prognosis

Much of the management of allergic asthma is similar to other types of asthma. Treatment consists of controlling the underlying inflammatory process with inhaled corticosteroids and using inhaled short acting (for acute attacks) and using leukotriene modifiers long acting (controller) bronchodilators when indicated. Please see the general asthma chapter in this book and the following Tables 1.2 and 1.3 for further details. Most therapies are not specific for those that have allergic asthma; however, avoidance, omalizumab, immunotherapy and leukotriene modifiers seem to have a great role in treatment of allergic asthma. Allergen sensitivity to perennial allergens has been associated with asthma severity [8]. Therefore, decreasing asthma triggers including the removal of the offending allergens, if possible, is preferred. This can, in many cases, improve the asthma or potentially, in some cases, eliminate it. Since IgE plays a pivotal role in the pathology of allergic asthma, treatment with anti-IgE therapy or omalizumab is a unique pharmacologic intervention. Its effects are multifactorial and include prevention of IgE from binding the IgE receptor (high and low affinity), resulting in a decrease in FceR1 receptors, and ultimately decreased

Table 1.2 Acute treatments for asthma

Rescue treatment	Mechanism of action	Effect
β_2-adrenergic receptor agonists	Activates adenylyl cyclase which increases C-AMP	Smooth muscle relaxation and bronchodilation
Anticholinergics	Blocks muscarinic cholinergic receptors which decreases C-GMP	Inhibits bronchoconstriction and mucus production

Table 1.3 Chronic treatments for asthma

Controller	Mechanism of action	Effect
Long acting β_2-adrenergic receptor agonist	Activates adenylyl cyclase which increases C-AMP	Smooth muscle relaxation bronchodilation
Anticholinergics	Blocks muscarinic cholinergic receptors which decreases C-GMP	Inhibits bronchoconstriction and mucus production
Corticosteroids	Up regulation/inhibition of proteins	Anti-inflammatory
Anti-leukotrienes	Block leukotriene receptor or decrease leukotriene production	Reduces bronchoconstriction decrease inflammation
Theophylline	Phosphodiesterase inhibitor which increases C-AMP	Anti-inflammatory
Anti-IgE	Blocks and down regulates IgE receptor	Block mediator release from basophils and mast cells

release of mast cell mediators and decrease production of IgE. Other potential treatments include immunotherapy to a specific allergen which attempts to induce tolerance to allergens and an overall greater TH_1 type of response. Lastly, leukotriene modifiers seem to have a greater affect in children with mild asthma and those who have allergic disease [10].

Prognosis typically depends on the individual's susceptibility to airway remodeling with unchecked inflammation. For example, some individuals will have minimal remodeling with a prolonged inflammatory response. Conversely, airway remodeling can be seen with minimal underlying inflammation; therefore, the prognosis is patient specific [6]. Ultimately, asthma is a complex chronic disease state where the culmination of genetics and the patient's predisposition to having an exaggerated immune response to environmental exposures determine the overall clinical prognosis.

Questions

1. What are the most common findings on pulmonary function studies in a patient with asthma?

   (a) Low FVC
   (b) Low FEV1/FVC
   (c) Decrease reserve volume
   (d) Low D_{LCO}

2. Which component of the immune system seems to play the most important role in allergic asthma?

   (a) TH_1 cells
   (b) TH_2 cells
   (c) T regulatory cells
   (d) T 17 cells

3. Regarding the mechanism of omalizumab, which of the following is partly responsible for its observed pharmacologic response?

   (a) Omalizumab decreases basophil FcεRl expression
   (b) Omalizumab binds free IgM in the circulation
   (c) Omalizumab prevents IgG from binding to its receptor
   (d) FcεRl expression is down regulated on epithelial cells

4. Sensitization to which of the following environmental allergen is thought to be most commonly associated with the development of allergic asthma?

   (a) Dust mite
   (b) Tree pollen
   (c) Ragweed
   (d) Peanut

5. Regarding the genetics of asthma which of the following is most correct?

   (a) There is likely a single dominant gent that will emerge as the cause
   (b) First-degree relatives of patients with asthma have no increased risk
   (c) Both genetic and environmental factors seem to be important
   (d) There seem to be few ethical differences in genetic predisposition to developing asthma

6. Peak flow testing has been shown to be most helpful in what setting?

   (a) COPD exacerbation
   (b) For patients with concordant symptoms and FEV_1
   (c) Serially to determine prognosis of acute asthma attack
   (d) Measured 120 min after treatment

7. Leukotriene modifiers seem to have a greater effect on which population?

   (a) Nonatopic individuals
   (b) Children
   (c) Adults
   (d) Elderly

8. Which of the following is a phosphodiesterase inhibitor which increases C-AMP?

   (a) Montelukast
   (b) Albuterol
   (c) Prednisone
   (d) Theophylline

9. Exhaled nitric oxide is an indirect marker of what type of airway inflammation?

   (a) Eosinophilic
   (b) Neutrophilic
   (c) Basophilic
   (d) Mast cell activity

10. Which of the following is *not* typically found in the sputum of patients with asthma?

    (a) Charcot-Leyden crystals
    (b) Curshmann's spiral
    (c) Heinz bodies
    (d) Creola bodies

Answer key: 1. (b), 2. (b), 3. (a), 4. (a), 5. (c), 6. (c), 7. (b), 8. (d), 9. (a), 10. (c)

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Chapter 2
Allergic Bronchopulmonary Aspergillosis

Nelson Ferrer, Samuel Krachman, and Gilbert D'Alonzo

Abstract Allergic bronchopulmonary aspergillosis (ABPA) is a complex hypersensitivity reaction in the lungs that occurs in susceptible individuals characterized by difficult to control asthma and a progressive decline in lung function if left untreated. Here we present two different challenging cases that illustrate some of the most important diagnostic and treatment aspects of ABPA.

Keywords Allergic bronchopulmonary aspergillosis • IgE • Bronchiectasis • Asthma

Case 1 Exertional Dyspnea and Wheezing

History of present illness: A 46-year-old African/American woman presented to the office in late December with a 1-month history of shortness of breath with minimal exertion and wheezing. Her illness evolved from an initial non-productive cough and rhinorrhea with no fever; at the same time her husband and son had flu-like symptoms. She went to see her allergist, who prescribed inhaled budesonide twice daily and inhaled albuterol PRN. She had minimal improvement with this regime. After 2 weeks, her cough became productive of green sputum and she was started on amoxicillin/clavulanate and an oral prednisone taper. Her sputum production decreased, but she still required inhaled albuterol 4–5 times/day.

Past medical and surgical history: History of "allergies" and eczema as a child with suspected asthma which she outgrew as a teenager. During the second trimester of a

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pregnancy she had an asthma exacerbation and she was treated with albuterol in the emergency department and discharged home the same day. During the past 2 years she has had allergic rhinitis and has been receiving weekly allergy shots. She denies a history of pneumonia, tuberculosis (TB) or TB exposure and she had a negative PPD in the past. Her surgical history includes a uterine myomectomy and a C-section. She has no drug allergies.

Family history: Her mother is alive and in good health at age 71 years old. Her father is the same age and has hypertension and colon cancer that is in remission. A son has a history of asthma.

Social and occupational history: She has done office work as an administrator most of her life and denies any significant occupational exposure relevant for lung disease. She is a lifelong non-smoker and does not use alcohol or illicit drugs. She has a dog at home, wall-to-wall carpeting on the second floor, and she changes her bed sheets regularly. There has not been any recent travel history beyond where she lives in the Northeastern United States.

Current medications: Inhaled albuterol and budesonide, and guaifenesin syrup.

Review of systems: Positive for cough, shortness of breath with minimal exertion, mild nasal congestion and chest tightness. No postnasal drip. A review of cardiac, gastrointestinal or genitourinary symptoms was negative.

Physical examination: Her pulse was 83 beats/min, respiratory rate 16 breaths/min, blood pressure 130/88 mmHg, and pulse oximetry was 100% while breathing room air. She was afebrile and in no acute distress. Her ears had normal tympanic membranes and her nose revealed congested inferior turbinates bilaterally. Her mouth and throat was negative for erythema and exudates. Auscultation of her lungs was clear with normal breath sounds. The rest of her physical examination was within normal limits.

Diagnostic testing: A chest x-ray done 1 week prior to her visit showed a prominent right pulmonary artery but no parenchymal abnormalities.

Impression: Dyspnea on exertion likely secondary to underlying asthma or post-viral hyper-reactive airways with an allergic rhinitis component.

Plan: She was advised to discontinue inhaled budesonide, and begin inhaled fluticasone/salmeterol 250/50 twice daily, montelukast 10 mg daily and intranasal mometasone daily. As needed albuterol was continued. Complete pulmonary function testing (PFT) was ordered with follow-up visit arranged for 3 weeks.

Clinical course: A day after her initial visit, the patient had pulmonary function testing which did not show airflow obstruction, an inhaled bronchodilator response, ventilatory restriction or lung air trapping. Over the next 3 weeks, the patient's cough got worse; she developed malaise and increased purulent nasal secretions and sputum production. Over this period of time her dyspnea on exertion did not improve and she was never febrile. Her physical examination at that time revealed that she had signs of lung consolidation in the right base, both egophony and dullness to percussion.

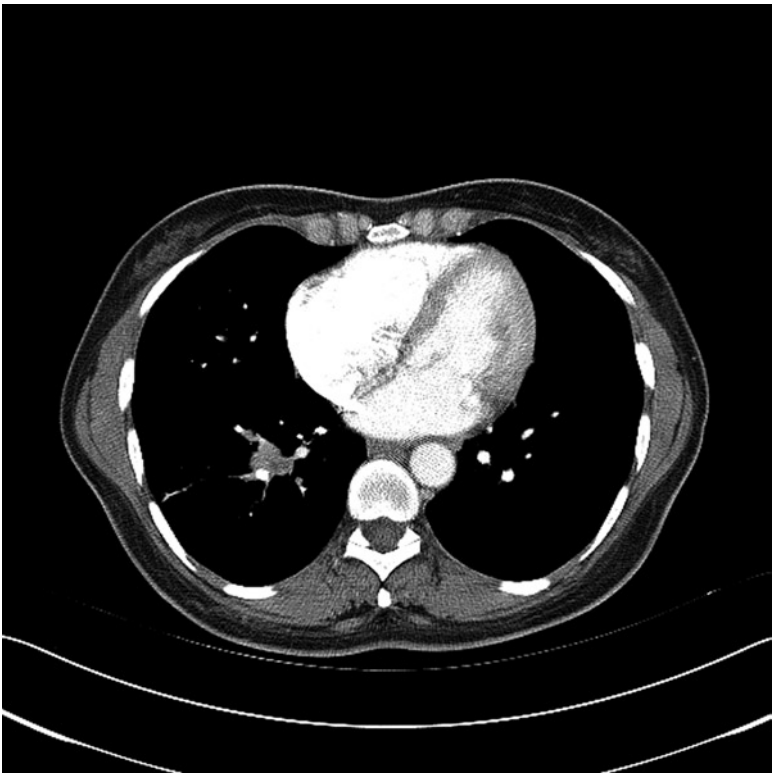

Fig. 2.1 Case 1 CT of the thorax showing an ill-defined soft tissue density at the right base with distal atelectasis and regional hilar lymphadenopathy with surrounding interstitial thickening

Workup

A CT of the sinuses was ordered, revealing complete opacification of the left maxillary sinus and left osteomeatal complex. A CT of the chest (see Fig. 2.1) showed an ill defined soft tissue density at the right base with distal atelectasis and regional hilar lymphadenopathy with surrounding interstitial thickening. Oral cefuroxime was started, a PPD was placed, and sputum smear and cultures for bacteria, AFB and fungi were collected. Blood tests were sent and a skin-prick test for *Aspergillus fumigatus* was placed. See Table 2.1 for results.

With Presented Data, What Is Your Working Diagnosis?

This 46-year-old woman presented with a 2-month history of cough, dyspnea on exertion, episodic wheezing and then a recent increase in sputum production with significant blood eosinophilia. Her CT of the chest showed a right lower lobe

Table 2.1 Case 1 laboratory findings

Test	Results	Normal range
WBC	10.7	4–11 k/mm^3
Hemoglobin	12.7	11.5–16 g/dL
Platelets	274	140–400 k/mm^3
Lymphocytes	22.1	20–44%
Monocytes	5.2	2–9%
Granulocytes	40	50–75%
Eosinophils	32.3	1–5%
Glucose	78	<110 mg/dL
BUN	9	7–25 mg/dL
Creatinine	0.8	<1.2 mg/dL
Electrolytes	Normal	
Liver function tests	Normal	
Sputum culture	Normal respiratory flora	
AFB smear	Negative × 3	
AFB culture	Negative	Negative
p-ANCA	Negative	Negative
c-ANCA	Negative	Negative
ANA	Negative	Negative
AFB culture	Negative	Negative
Fungal culture	*Aspergillus fumigatus*	Negative
IgE (total)	465	0–180 IU/mL
IgE *A. fumigatus*	387	0–180 IU/mL
IgG *A. fumigatus*	1,870	565–1,765 mg/dL
*Aspergillus s*kin-prick test	Positive	Negative

infiltrate leading us to the diagnosis of right lower lobe pneumonia with atelectasis and a CT of the sinuses showed evidence of acute or chronic sinusitis.

Differential diagnosis: The differential diagnosis includes sarcoidosis, histoplasmosis, coccidiomycosis, tuberculosis, Löffler's syndrome, Wegener's granulomatosis, Churg–Strauss syndrome, acute or chronic eosinophilic pneumonia and allergic bronchopulmonary aspergillosis (ABPA).

What Is Your Diagnosis and Why?

Sarcoidosis: Although the patient had significant peripheral blood eosinophilia, which can be seen in 25% of patients with sarcoidosis, malaise and shortness of breath, the patient lacked hilar adenopathy, pulmonary nodules, ground glass opacification or other radiologic findings associated with sarcoidosis.

Histoplasmosis/Coccidiomycosis: The patient did not have any history of immune deficiency, did not engage in any of the activities associated with exposure to

histoplasma or *coccidioides*, including an appropriate travel history, and had no articular or skin manifestations.

Tuberculosis: Primary tuberculosis can present with focal consolidation and eosinophilia in <10% of the cases, but there was no pleural effusion or nodules, she had no history of exposure or risk factors for tuberculosis and her PPD, was negative. Her sputum cultures were reported to be negative after 6 weeks.

Löffler's syndrome: The patient had potential exposure to roundworms because of her history of having a dog at home, but Löffler's syndrome tends to resolve spontaneously and this patient had a progressive, non-resolving clinical course.

Churg–Strauss syndrome: The patient had a history of asthma, peripheral eosinophilia associated with sinus and pulmonary symptoms, but she had no neurologic or skin involvement and her perinuclear antineutrophil cytoplasmic antibody (P-ANCA) tests were negative.

Wegener's granulomatosis: This is another autoimmune disease that has both sinus and pulmonary manifestations. However, she did not have any evidence of cavitary lesions or nodules in her lungs, there was no history of renal involvement and her diffuse antineutrophil cytoplasmic antibody (C-ANCA) was negative.

Acute eosinophilic pneumonia: This disease has an acute clinical course of progressive dyspnea, bilateral pulmonary infiltrates and progressive respiratory failure. Peripheral eosinophilia is typically absent.

Chronic eosinophilic pneumonia: This disease is associated with peripheral eosinophilia, and its clinical course is subacute like in our patient. It presents with weight loss, night sweats, fever, breathlessness and asthma. The chest x-ray typically has peripheral infiltrates, which has been described as a photographic negative pulmonary edema, which was not seen in our patient.

ABPA: Our patient presented with a significant history of asthma, pulmonary infiltrates on the chest CT peripheral blood eosinophilia of >1,000 cells/mL, immediate skin reactivity to *Aspergillus fumigatus*, elevated specific IgE and IgA to *Aspergillus fumigatus.*

Clinical Course: After results of specific testing arrived, a diagnosis of ABPA was made. Therapy with prednisone 60 mg/day for 14 days was started, as well as itraconazole 200 mg twice daily. Two weeks after therapy was started, the patient was seen again, with marked improvement in symptoms. She denied any further shortness of breath, cough, sputum production, fever, chills; and her nasal symptoms also resolved. A chest CT scan 8 weeks after therapy was initiated (see Fig. 2.2), which demonstrated almost complete resolution of the right basilar consolidation. Her serum IgE level and blood eosinophil count returned to normal. Over the next 8 months, she received itraconazole and her oral steroids were tapered to a low daily dose. Her symptoms have not recurred.

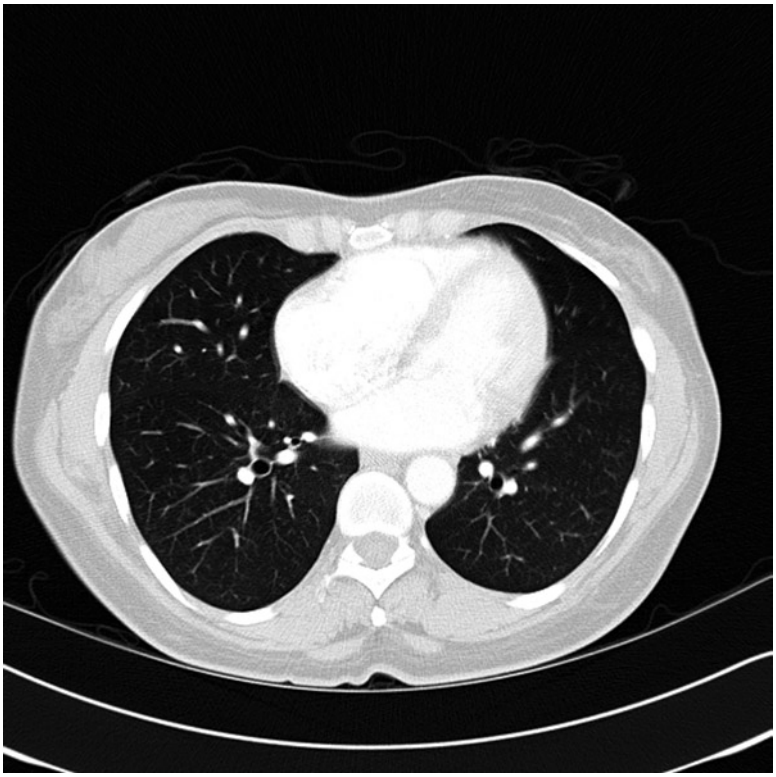

Fig. 2.2 Case 1 CT of the thorax 8 weeks later demonstrated almost complete resolution of the right basilar consolidation

Summary: Our patient presented with several diagnostic challenges. The first being that on initial evaluation, she had no evidence of pulmonary infiltrates on physical exam and chest x-ray. The second diagnostic challenge was that her total IgE level was elevated (465 IU/mL), but well below the value that is considered (>1,000 IU/mL) diagnostically optimal for ABPA. Lastly, there was no evidence of bronchiectasis on her chest CT prior to therapy. Her dramatic clinical response to therapy, as well as her subsequent normal chest CT 8 weeks after initiating therapy confirms the final diagnosis of ABPA-S (serologic, without bronchiectasis).

Case 2 Persistent Cough

History of present illness: A 54-year-old Caucasian woman presents to our office with a series of abnormal chest CT scans and requests a second opinion. Her history started approximately 1 year prior when she was evaluated at her local hospital for

persistent symptoms of cough and sputum production after an asthma exacerbation. An initial chest x-ray performed at the time revealed a right upper lobe consolidation with a questionable mass. A subsequent chest CT and PET scan confirmed the presence of a mass in the right upper lobe with enhanced metabolic activity. Bronchoscopic examination with transbronchial biopsies did not show definitive evidence of cancer, and her cultures grew *Aspergillus flavus*. While surgical diagnostic options were considered, antifungal therapy was started and a repeat chest CT 3 months later revealed resolution of the mass. At the time of our initial evaluation, she was having intermittent wheezing that required albuterol use an average of three times a week, as well as nasal congestion.

Past medical and surgical history: Allergies to a variety of environmental allergens since childhood, when she received immunotherapy. She had a history of hypertension, moderate persistent asthma, gastroesophageal reflux disease (GERD), hiatal hernia and chronic sinusitis. She had sinus surgery twice in the past, which consisted of a polypectomy and mucus impaction removal.

Family history: Her parents are deceased; both had a history of coronary artery disease. She has three sons, one with a history of allergies and another with a history of immune thrombocytopenia. The third son has no medical problems.

Social and occupational history: She has been working as a cashier for the past 4 years in a hardware store. She is a lifelong non-smoker and does not use alcohol or illicit drugs. She does not have a history of TB exposure or international travel.

Current medications: Albuterol, montelukast, voriconazole, omeprazole.

Review of systems: Occasional non-productive cough. No rhinorrhea, post-nasal drip, chest pain, shortness of breath, hemoptysis, weight loss, anorexia, fever or night sweats. She denied active GERD symptoms.

Physical examination: She was afebrile with a pulse of 86 beats/min, blood pressure 140/80, a respiratory rate of 14 and pulse oximetry was 99% while breathing room air. She was alert and cooperative, in no acute distress. Examination of ears and throat was normal; she had bilateral nasal congestion. Her neck was supple and without lymph node enlargement or jugular vein distention. Examination of the thorax demonstrated symmetric expansion and her lungs were clear to auscultation. There was no cyanosis or clubbing of her fingers; the rest of the physical examination was unremarkable.

Diagnostic testing: Six CT scans of the chest done during the previous year revealed bronchiectasis of the right upper lobe with associated cystic changes and various degrees of mucous impaction. A most recent CT had significant improvement of mucous impaction. There was no evidence of a mass (see Fig. 2.3).

Impression: Moderate persistent asthma with right upper lobe bronchiectasis.

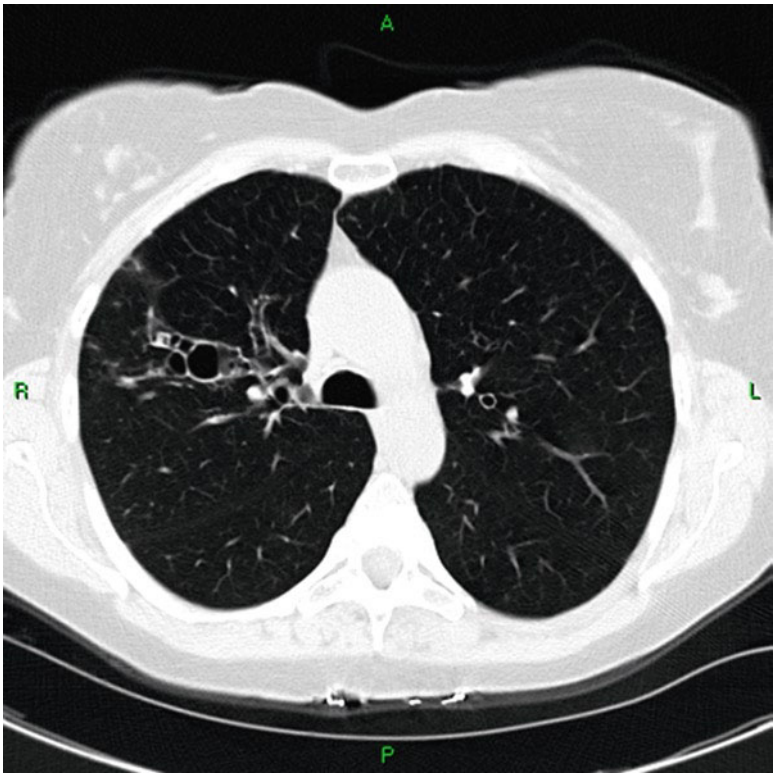

Fig. 2.3 Case 2 CT of the thorax, which shows bronchiectasis of the right upper lobe with associated cystic changes and no signs of mucous impaction

Plan: The patient was advised to discontinue the montelukast, start inhaled budesonide twice daily and intranasal fluticasone daily.

With Presented Data, What Is Your Working Diagnosis?

This 54-year old woman with a past medical history of asthma and a prior right upper lung mass-like consolidation that improved with treatment was evaluated for a second opinion. At the time of the initial evaluation, she had evidence of bronchiectasis on her latest chest CT.

Differential diagnosis: Given her history and positive finding of bronchiectasis on her latest chest CT, the differential diagnosis included intraluminal obstruction, tuberculosis, atypical mycobacterial infection, hypogammaglobulinemia, Wegener's granulomatosis, sarcoidosis and ABPA.

Table 2.2 Case 2 laboratory results

Test	Results baseline	Results at 6 months	Normal range
WBC	7.3	8.4	4–11 k/mm^3
Hemoglobin	12.4	11.9	11.5–16 g/dL
Platelets	251	300	140–400 k/mm^3
Lymphocytes	38	21	20–44%
Monocytes	4	2	2–9%
Granulocytes	54	53	50–75%
Eosinophils	4	24	1–5%
Glucose	98	105	<110 mg/dL
BUN	14	12	5–15 mg/dL
Creatinine	0.7	0.8	<1.4 mg/dL
Electrolytes	Normal		Normal
Liver function tests	Normal	Normal	Normal
Total IgA	Normal		Normal
Total IgM	Normal		Normal
Total IgG	Normal		Normal
Total IgD	Normal		Normal
c-ANCA	Negative		Negative
IgE (total)	1,304 IU/mL	1,773 IU/mL	0–180 IU/mL
IgE *A. flavus*	16.07 IU/mL		<0.1 IU/mL
A. flavus skin-prick test	Positive		Negative
PPD	Negative		Negative
Atypical mycobacteria culture	Negative		Negative

Workup

Full pulmonary function testing (PFT), a CBC with measurement of total IgE levels, specific IgA and IgG for *Aspergillus flavus* and a skin-prick test using *Aspergillus flavus* antigens were ordered. A PPD was placed, a bronchoscopy was done and bronchio-alveolar lavage (BAL) was sent for culture of atypical mycobacteria. Her lab results are presented on Table 2.2.

What Is Your Diagnosis and Why?

Intraluminal obstruction: Bronchoscopic examination of the airway did not reveal any signs of endobronchial obstruction or foreign bodies.

Tuberculosis: The patient had a negative history of exposure to tuberculosis, and her PPD was negative. BAL was negative for tuberculosis.

Atypical mycobacteria: Cultures from BAL fluid were negative for atypical mycobacteria.

Hypogammaglobulinemia: With the exception of a high IgE level, the rest of her immunoglobulin profile was within normal limits.

Wegener's granulomatosis: The patient did not have any symptoms of sinus or renal disease, and her ANCA serology was negative.

Sarcoidosis: Upper lobe bronchiectasis can be associated with sarcoidosis, but serial imaging failed to demonstrate hilar adenopathy and upper lobe infiltrates after the initial presentation. Sarcoidosis in remission was still a diagnostic possibility until the rest of the workup pointed to a more appropriate diagnosis.

ABPA: The patient had a history of asthma, evidence of bronchiectasis, high total IgE levels, positive skin test to *Aspergillus flavus* antigen, prior right upper lobe infiltrates that cleared and specific IgE antibodies against *Aspergillus flavus.* Given the evidence, her diagnosis was narrowed to ABPA with bronchiectasis (ABPA-CB).

Clinical course: The patient presented 3 months after her initial evaluation. In the interim, she had PFT done, which revealed a moderate obstructive defect with significant bronchodilator response, no ventilatory restriction or carbon monoxide diffusion impairment. She complained of occasional wheezing that required albuterol about once a week; she stopped her voriconazole 1 month prior to her visit and at that that point she was advised to continue the inhaled budesonide twice daily and albuterol PRN and to get monthly IgE levels. Three months later, the patient had increased shortness of breath with sputum production and wheezing, the total IgE levels increased to 1,773 IU/mL (see Table 2.2) and a chest x-ray revealed a right upper lobe infiltrate. An ABPA exacerbation was diagnosed and she was started on a high daily dose of oral prednisone along with itraconazole 200 mg twice daily. The patient's symptoms improved after 6 weeks of therapy and the right upper lobe infiltrate on chest x-ray resolved. She was re-evaluated in the office at that time she expressed concerns about her high dose of steroids because of weight gain and the risk of osteoporosis. She was advised to continue taking the steroids at a lower day dose, but over the next 3 months the patient tapered herself off steroids and experienced an increase in malaise, intermittent fevers and her total IgE level remained elevated. Steroids and itraconazole where re-started and over the next 8 months the patient's symptoms slowly resolved and her IgE level decreased to a patient specific low of 331 IU/mL. She stopped using itraconazole, but in the subsequent year, attempts to decrease prednisone below 10 mg/day resulted in symptoms of asthma exacerbation without any further increases of IgE or appearance of x-ray infiltrates.

Summary: This case presented a diagnostic challenge on initial evaluation because a diagnosis had to be made based on a prior not witnessed clinical picture with the patient being mostly asymptomatic. After the diagnosis was confirmed, management became difficult because of serial courses of partial, ineffective treatments. The patient had valid concerns regarding the long-term side effects of her medications, but as exacerbations became progressively more difficult to control, she became more compliant and her ABPA finally came under control. Her IgE levels finally stabilized at a relatively low level, but her clinical state was systemic steroid

dependent. On subsequent PFT and chest CT there was no evidence of fibrosis, ultimately settling her diagnosis as stage IV ABPA-CB.

Discussion

Definition: ABPA is a complex hypersensitivity reaction in the lungs of susceptible individuals caused by an exaggerated response to antigens produced by *Aspergillus* species. Hinson et al. [1] in the United Kingdom first described it in 1952 in a series of eight patients who had significant occupational exposure to high allergen loads, asthma and peripheral eosinophilia. Since then, it has been estimated that about 13% of the patients with asthma attending specialty asthma clinics [2] and 1–15% of patients with cystic fibrosis [3] have ABPA. The prevalence is typically higher in developed countries, likely reflecting heightened clinician awareness and better diagnostic tools.

Presentation: The typical patient is immunocompetent and in their third or fourth decade of life. There is no gender predilection and over 90% of patients in published series have a history of asthma. During acute presentation, patients complain of dyspnea on exertion, wheezing and intermittent fevers. Chronic cough containing mucous plugs and hemoptysis are also seen regularly. Physical examination can be normal in asymptomatic patients, but in acute exacerbations patients can have wheezing and signs of lung consolidations. Patients in the late stages of the disease can have a loud S2 consistent with pulmonary hypertension or dry crackles suggestive of pulmonary fibrosis.

Pathophysiology: Patients with ABPA usually have impaired mucous clearance (patients with CF) and high degrees of atopy (asthmatic patients), but multiple studies have identified specific genetic defects involved in the development of ABPA through different genetic pathways. One of these affected pathways involve mutations in the cystic fibrosis transmembrane receptor (CFTR) in patients without CF [4] that can either predispose to bronchiectasis or promote immune response to *Aspergillus*. Another defect includes HLA-DR 2/5 allele mutations that provide either susceptibility or protection in ABPA [5]. Genetic polymorphism in surfactant protein A1 (SP-A1) and SP-A2 are correlated with a marked increase in total IgE antibodies, peripheral eosinophilia and a decrease in FEV1, thus contributing to increased severity of disease [6].

The cascade of events that result in ABPA is complex and is not completely understood. In genetically susceptible individuals, inhaled *Aspergillus fumigatus* conidia germinate in the airway and release spores, thus becoming a constant source of antigen that reacts with the host's immune system. These antigens contribute to the two types of immune responses seen in ABPA: an immediate type I hypersensitivity, where the antigens react with cell bound IgE causing mast cell and eosinophil degranulation and a type III hypersensitivity reaction involving immune complexes between fungal antigens and IgG that activates complement, promoting tissue injury. There is also a humoral response that occurs in the bronchial associated lymphoid tissue (BALT), where activated B-lymphocytes produce *Aspergillus* specific IgE and IgA. Finally,

there are direct interactions between the released fungal products (proteolytic enzymes) that break down airway epithelial cells and expose extracellular matrix, with the subsequent production of pro-inflammatory cytokines. All these mechanisms contribute to continuous inflammation that result in the bronchial wall injury and airway remodeling that leads to airway hyperreactivity and bronchiectasis.

Workup: Laboratory findings in ABPA include an absolute increase of eosinophils in the complete blood count (CBC), which was reported to be >1,000 cells/μL in 47% of patients in a recent series [7]. Sputum cultures are of limited value, since positive cultures for *Aspergillus* sp. are non-specific for ABPA. Total serum IgE levels are useful for both diagnosis and follow up of patients with ABPA. IgE levels >1,000 IU/mL is one of the major criteria for diagnosis; a decline in the total IgE level after treatment with glucocorticoids is consistent with a clinical response.

The *Aspergillus* skin test is used to determine an immediate type of hypersensitivity; all patients with ABPA have a positive test, defined as the appearance of erythema and an edematous wheal after 1 min of application of the test, reaching a maximum induration within 20 min. It is important to point out that between 20% and 30% of all asthmatic patients that do not have ABPA have a positive skin test [8]. Specific serum IgE, IgA and IgG antibodies against *Aspergillus* measured by ELISA are characteristic of ABPA. IgG antibodies that react against *Aspergillus* antigens and precipitate are supportive but not diagnostic of ABPA.

Radiologic findings in ABPA vary depending on the clinical stage of the disease. Chest x-ray can have fleeting infiltrates in the upper and middle lobes if the patient is experiencing an exacerbation of the disease; mucoid impaction ("gloved finger" opacities) and bronchiectasis are also seen; a reticular pattern indicating fibrosis is less commonly seen. A CT scan of the chest provides more information than a chest x-ray; central bronchiectasis, focal consolidations and atelectasis are common findings, as well as mucoid impactions. A mosaic pattern is also recognized, indicating air trapping. Cavitations and interstitial thickening are seen in the later stages of the disease. Spirometry reveals an obstructive defect with bronchodilator response in approximately half of the patients; lung volumes measurement can reveal an increase in residual volume, indicating air trapping. A restrictive pattern can also be seen in the more advanced stages of the disease.

Diagnostic criteria and staging: No single test establishes the diagnosis of ABPA. A combination of clinical, radiographic and laboratory criteria for the diagnosis of ABPA was originally proposed by Rosenberg et al. [9] and further refined by Patterson et al. [10]. These criteria include history of asthma, peripheral blood eosinophilia >1,000 cells/mL, immediate skin reactivity to *Aspergillus* sp. antigens, precipitating antibodies against *Aspergillus* sp., serum IgE concentrations of >1,000 IU/mL, elevated specific serum IgE or IgA against *Aspergillus* sp., lung infiltrates on chest x-ray or chest CT and central bronchiectasis. While the presence of 6/8 major criteria makes the diagnosis of ABPA almost certain, there is no conclusive evidence of the minimum number of criteria that needs to be present in order to make the diagnosis.

The natural history of ABPA is poorly understood, but the five stages described by Patterson et al. [10] provide a useful framework of reference (see Table 2.3).

Table 2.3 ABPA stages

Stages	Description	Clinical picture
I	Acute phase	Fever, malaise, cough, wheezing
II	Remission	Asymptomatic
III	Exacerbation	As in acute phase
IV	Steroid-dependent asthma/ABPA	Increase IgE from baseline, recurrent symptoms with steroid taper
V	Fibrotic	Restrictive lung disease, pulmonary hypertension

Adapted from Patterson et al. (see reference [10])

Patients do not progress from one stage to the other sequentially; treatment decisions, as well as overall prognosis will depend on the patient's stage.

Treatment: There are two mainstays in the treatment of ABPA: oral glucocorticoids, which decrease the inflammatory response; and antifungal agents, which control the total fungal burden in the airway, thereby reducing the stimulus for the allergic reaction. The steroid dose is not clearly established, but better outcomes are associated with higher doses. A treatment regimen of prednisolone at 0.75 mg/kg/day for a total of 6 weeks, then 0.5 mg/kg/day for 6 weeks and then tapered by 5 mg every 6 weeks for a total duration of treatment of 6–12 months has been associated with complete relapse in 109 out 126 patients [7]. The use of inhaled corticosteroids potentially has a role in asthma control once oral steroid has been tapered. An adequate treatment response is defined by a total IgE level reduction between 35% and 50% after 6 weeks of treatment. Follow up should include serial IgE to try to establish a baseline value for the patient; a doubling of this value would indicate an exacerbation.

Oral antifungal agents have been evaluated for the treatment of ABPA. Currently, itraconazole is recommended at 200 mg bid for 16 weeks and the 200 mg daily for 16 weeks [11]. Voriconazole is also being evaluated in the treatment of ABPA, but its efficacy has not been compared directly to itraconazole. Liver function tests should be checked regularly while on antifungal therapy and drug interactions should be monitored, especially between itraconazole and gastric acid blocking agents. The anti-IgE agent omalizumab has been used effectively in the treatment of a young patient with CF and steroid dependent ABPA [12].

Questions

Case 1

1. Which one of the following is an important key element in the past medical history of a patient in which ABPA is considered as a diagnostic possibility?

   (a) History of asthma
   (b) History of cystic fibrosis
   (c) Immunocompetent host
   (d) All of the above

2. Which one of the following hypersensitivity reactions is not associated with the pathogenesis of ABPA?

   (a) Type I hypersensitivity
   (b) Type II hypersensitivity
   (c) Type III hypersensitivity
   (d) None of the above

3. Which pulmonary function test finding is most likely to be found in a patient with a diagnosis of ABPA?

   (a) Bronchoreversibility
   (b) Obstructive pattern
   (c) Restrictive pattern
   (d) Decreased diffusion capacity

4. Which one of the following tests is the best one for screening for ABPA?

   (a) Positive skin prick testing with *Aspergillus* antigens
   (b) Total serum IgE level >1,000 IU/mL
   (c) Total blood eosinophils >1,000 cells/μL
   (d) All of the above
   (e) None of the above

5. Common chest CT findings in early ABPA include:

   (a) Large pulmonary arteries
   (b) Fleeting pulmonary infiltrates
   (c) Mosaic pattern
   (d) All of the above

Case 2

6. Which stage in the clinical course of ABPA is considered irreversible?

   (a) Stage I
   (b) Stage III
   (c) Stage IV
   (d) None of the above
   (e) All of the above

7. What percentage of patients with asthma that do not have ABPA have a positive *Aspergillus* skin prick test?

   (a) 1–5%
   (b) 10–20%
   (c) 20–30%
   (d) 40–50%

8. Which one of the following clinical entities is not usually associated with peripheral eosinophilia?

   (a) Sarcoidosis
   (b) Löffler syndrome
   (c) Churg–Strauss disease
   (d) None of the above
   (e) All of the above

9. Which of the following tests is the most sensitive for monitoring treatment of ABPA?

   (a) Total IgE level
   (b) Chest CT
   (c) Pulmonary function testing
   (d) Total peripheral blood eosinophil count

10. Which one of the following represents an advantage of treatment of ABPA with itraconazole?

    (a) Steroid sparing effect
    (b) Decreased antigenic load
    (c) Increased gastric absorption with a high pH
    (d) a + b
    (e) All of the above

Answer key: 1. (d), 2. (b), 3. (b), 4. (e), 5. (b), 6. (d), 7. (c), 8. (d), 9. (a), 10. (d)

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Chapter 3
Hypersensitivity Pneumonitis

Rachna Shah and Leslie Grammer

Abstract Hypersensitivity pneumonitis (extrinsic allergic alveolitis) is characterized by a non-IgE mediated inflammation which can progress to disabling or even fatal end-stage lung disease. It is caused by repeated inhalation of non human organic dust including birds, agricultural dusts, and molds. Hypersensitivity pneumonitis is treated with avoidance to the causative antigen and corticosteroids. We present two challenging cases of hypersensitivity pneumonitis.

Keywords Antibody to pheasant • Chronic cough • Farmer's lung • Hypersensitivity pneumonitis • Hot tub lung • Recurrent pneumonia • Ventilation pneumonitis

Case 1

A previously healthy 11-year-old boy presented to the allergist for a chronic cough [1]. Symptoms started 2 years ago and included a nonproductive cough that occurred primarily from May to June. This year, his cough continued into August which prompted the evaluation by the allergist. His cough was nonproductive, constant through the day, and would not wake him up at night. He also had symptoms of chest heaviness but no symptoms of wheezing. Mom noted that he seemed more fatigued and could not keep up with the other kids during physical activity. Patient denies fevers, chills, weight loss, or night sweats. No triggers were identified for the cough.

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Table 3.1 Lab results case 1

Test	Result	
Skin test	Trees	Negative
	Grasses	Negative
	Ragweed	Negative
	Molds (including *Aspergillus*)	Negative
	Dog	Negative
	Cat	Negative
	Rabbit	Negative
	Dust mite	Negative
Purified protein derivative (PPD)	Negative	
CBC		
Hemoglobin	12.4 g/dL	(11.6–15.4 g/dL)
Hematocrit	40.1%	(34.0–45.0%)
Platelets	328 k/uL	(140–390 k/uL)
WBC	6.1 k/uL	(3.5–10.5 k/uL)
PMNs	59%	(34–73%)
Lymphocytes	37%	(15–50%)
Monocytes	2%	(5–15%)
Eosinophils	1%	(0–8%)
Basophils	1%	(0–2%)
ESR	2 mm/h	(3–13 mm/h)

The environmental history was significant for a great deal of mulch around the house. The patient's father also raised pheasants and the patient participated in their care. The patient would help clean their cages and feed the birds. He would spend at least 2 h with these birds. The incubators for the birds were moved into the basement from May to July and the bird cages were moved into the garage that was 10 ft away from the house. The patient also had a rabbit and a bird that were kept outside. There was no significant past medical history or family history.

On physical exam he was noted to be well appearing and in no acute distress. His blood pressure was 85/55 mmHg and pulse of 72 beats/min. His height and weight were appropriate for age. Through the exam he had numerous bouts of coughing. His conjunctiva were mildly injected, nasal turbinates were edematous with deep red mucosa, and no lymph nodes were palpated. Heart and lungs were clear on examination. No digital clubbing was noted.

Skin prick testing to aeroallergens, purified protein derivative (PPD) complete blood count, and sedimentation rate (ESR) were performed and results are summarized in Table 3.1.

With the Presented Data What Is Your Working Diagnosis?

Given the history of a chronic cough with negative skin test and normal lab results, the differential can be very broad. We can consider cough equivalent or cough variant asthma, hypersensitivity pneumonitis (HP) given history of exposure to birds,

chronic sinusitis presenting as a chronic cough, bronchiectasis, allergic bronchopulmonary aspergillosis (ABPA), cystic fibrosis, gastroesophageal reflux disease (GERD), B cell immunodeficiency, or cardiac disease. Patient had a negative skin test to *Aspergillus* making ABPA less likely. Cystic fibrosis is an autosomal recessive disorder and usually presents with pneumonia or bronchiectasis on chest radiograph. Though chest x-ray has not been done, the patient has no family history of cystic fibrosis and no history of pneumonia. This patient had no symptoms by history of GERD. B cell immunodeficiency usually presents with frequent sinopulmonary infections which were not elicited from this patient's history. There was no evidence based on history or physical exam that the patient has heart failure from cardiac disease. Further evaluation of asthma, hypersensitivity pneumonitis, and bronchiectasis was warranted.

Additional Workup

Chest x-ray, pulmonary function test, and evaluation of precipitating antibodies to mold and birds were completed. The chest x-ray demonstrated bilateral lower lobe patchy infiltrates with a reticulonodular pattern. Pulmonary function tests (Table 3.2) showed a reduction in FVC, TLC, and DLCO. There was no significant postbronchodilator reversibility. This was interpreted as either upper airway obstruction or poor effort due to the reduced PEFR that was out of proportion to other flows. It also demonstrated a reduction in total lung capacity, mild restriction, and severely reduced diffusing capacity [1]. Precipitating antibodies were positive to pheasant and pigeon.

Table 3.2 Pulmonary function test case 1

	Prebronchodilator	% Predicted	Postbronchodilator	% Predicted
FVC, L	*2.11*	*77%*	*2.15*	*78%*
FEV_1, L	2.11	88%	2.13	89%
FEV_1/FVC, %	99.76	113%	99.16	112%
$FEF_{25–75\%}$, L/s	3.22	117%	3.62	132%
PEFR L/s	4.04	52%	5.75	75%
TV, L	0.55	154%		
FRC, L	1.33	54%		
RV, L	0.57	73%		
TLC, L	*2.87*	*60%*		
DLCO	*17.66*	*61%*		

FVC forced vital capacity, FEV_1 forced expiratory volume in 1 s, $FEF_{25–75\%}$ forced expiratory flow 25–75%, *PEFR* peak expiratory flow rate, *TV* tidal volume, *FRC* forced residual capacity, *RV* residual volume, *TLC* total lung capacity, *DLCO* diffusion capacity

What Is Your Diagnosis and Why?

The patient was diagnosed with bird fancier's hypersensitivity pneumonitis. This diagnosis was supported by the history of chronic cough, strong environmental history, chest x-ray finding of bilateral lower lobe patchy infiltrates, low DLCO on PFTs, and positive precipitating antibodies to pheasant. Treatment included avoidance of pheasants and a course of oral and inhaled corticosteroids. Ten days after completing therapy, pulmonary function tests returned to normal.

Discussion

HP was first recognized by Ramazzini in 1713 in grain workers [2]. It is characterized by a non-IgE mediated inflammation which can progress to disabling or even fatal end-stage lung disease. A wide variety of inhaled organic dusts have been implicated in this disease [2]. Though the exact incidence of HP is unclear, it is known to be less prevalent than cryptogenic fibrosing alveolitis or sarcoidosis [3]. It is most commonly seen in men, especially during middle age [3].

The pathogenesis of HP is not fully understood. No animal models have paralleled human disease and most human studies have relied on bronchoalveolar lavage (BAL) samples. Proliferation of $CD8^{+}$T cells and increased production of antibodies, especially IgG, suggests that both the cellular and humoral immune systems play a role in the clinical manifestations of HP [4, 5]. Infiltrates and inflammation seen in HP usually consist of lymphocytes, plasma cells, and neutrophils [5]. Noncaseating granulomas, and in later stages interstitial fibrosis with collagen thickened bronchiolar walls, can be seen [5].

The diagnosis of HP requires known exposure to a cause of HP. There is no single confirmatory test for hypersensitivity pneumonitis; however, six significant predictors were identified that provide a 95% confidence interval. These include: (a) exposure to a known offending allergen; (b) positive precipitating antibodies to the offending antigen; (c) recurrent episodes of symptoms; (d) inspiratory crackles on lung auscultation; (e) symptoms occurring 4–8 h after exposure, and (f) weight loss [2, 6]. Symptoms of inspiratory crackles and dyspnea as the only criteria would have a probability of HP of less than 1%.

The clinical manifestation of HP can be divided into acute, subacute, or chronic forms. Acute HP occurs 4–12 h after intense exposure to the inciting allergen with symptoms that include fever, tachypnea, dyspnea, cough, and flu-like symptoms [2]. Symptoms resolve within 18–24 h with complete avoidance of the allergen. Subacute HP occurs gradually over several days to weeks and is marked by cough, dyspnea, and can progress to severe dyspnea and cyanosis [7]. Subacute HP can be difficult to define and may be a variant of the acute form of HP [7]. Chronic HP occurs over months with noted symptoms of cough, exertional dyspnea, fatigue, and weight loss [7].

In patients with suspected HP, initial tests would include a complete blood count, sedimentation rate, serum precipitating antibodies, chest x-ray, and pulmonary function tests [5]. In the acute form of HP, a left shift and elevated ESR can be seen. Serum precipitating antibodies are the hallmark immunologic response in HP. IgG and other classes of antibodies against the offending agent can be found in patients with HP [2]. With negative serum precipitants and a strong history, antigens prepared from the patient's environment may be used.

Imaging studies include chest film and high resolution CT scans. Abnormalities on chest film can be transient or permanent. In acute HP chest x-ray can show patchy, peripheral, bilateral interstitial infiltrates with a fine, reticulonodular pattern similar to acute pulmonary edema [2]. These findings can resolve spontaneously. In chronic HP fibrotic changes with patchy or random reticulation, traction bronchiectasis, and areas of emphysema may be seen superimposed on acute or subacute changes, typically sparing the lung bases [2]. CT scans can be helpful in evaluating vague parenchymal changes seen on chest x-ray. High resolution CT scans usually show ground glass opacities and small nodules located most commonly in the middle lobe in patients with HP.

Other studies to help diagnosis HP include pulmonary function tests and bronchoalveolar lavage (BAL). Pulmonary function tests can show restriction, obstruction, or both. DLCO is reduced in both the acute and chronic form of HP. When the diagnosis is not clear and other testing is normal, BAL may be necessary. BAL fluid can show primarily a lymphocytosis, with an increased ratio of $CD8^+$ T cells as compared to $CD4^+$ T cells in HP.

Treatment of HP primarily consists of avoidance of the causative agent. This can be done by removing the patient from the antigen either by relocation or by removing the antigen from the patient's environment. Acute and subacute HP can be treated with corticosteroids to help improve symptoms and reduce inflammation. A typical course of prednisone for an adult consists of a dose of 40–80 mg daily until clinical and laboratory improvements are observed. Then the dose is decreased stepwise every 1–2 weeks, by 5–10 mg/week over a period of 6 weeks. Equivalent doses of alternative day prednisone can also be used.

Case 2

A previously healthy 5-year-old boy presented to the allergist for evaluation of recurrent pneumonia [6]. Symptoms started 3 years ago and included coughing, wheezing, and crackles heard episodically on physical exam for the past 3 years. He never had a fever. Infiltrates and atelectasis were documented on chest x-ray for several of the episodes. He was treated with oral antibiotics, albuterol syrup, and prednisolone with temporary improvement in symptoms. The patient's family denied history of gastrointestinal upset, acid reflux, coughing after meals, ear or sinus infections, congenital abnormalities, or history of cystic fibrosis.

Table 3.3 Lab and study test results case 2

Test	Result	
Skin test	Dust mite	Positive
	Trees	Negative
	Grasses	Negative
	Ragweed	Negative
	Molds (including *Epicoccum*)	Negative
ESR	48 mm/h	(3–13 mm/h)
Serum precipitins	*Aspergillus*	Negative
	Thermoactinomyces	Negative
	Cephalosporium	Negative
	Avian proteins	Negative
Chest x-ray	Bilateral hilar enlargement and hyperinflation consistent with reactive airway disease	

Table 3.4 Pulmonary function test case 2

	Prebronchodilator	% Predicted	Postbronchodilator
FVC, L	*0.90*	*59%*	*Unchanged*
FEV_1, L	0.90	67%	Unchanged
FEV_1/FVC, %	100		Unchanged
$FEF_{25–75\%}$, L/s	1.50	87%	Unchanged
PEFR, L/s	2.16	103%	Unchanged

FVC forced vital capacity, FEV_1 forced expiratory volume in 1 s, $FEF_{25–75\%}$ forced expiratory flow 25–75%, *PEFR* peak expiratory flow rate

The environmental history was significant for parental smoking. The parents denied birds in the house, pets, basement flood, visible mold, or roof leakage. The family did not use a humidifier. There was no significant past medical history or family history.

On physical exam he was noted to have inspiratory and expiratory wheezing, rhonchi, and rales louder on the left than then right side. Oxygen saturation was 93% on room air. Wheezing improved with albuterol administration.

Skin prick test to aeroallergens, ESR, serum precipitating antibodies, chest x-ray, and pulmonary function tests were performed and the results are summarized in Tables 3.3 and 3.4.

With the Presented Data What Is Your Working Diagnosis?

Recurrent pneumonia is defined as greater than two episodes in a single year or greater than three episodes ever, with radiologic clearing between occurrences [8]. The majority of children with recurrent pneumonia have an identifiable underlying cause. In the differential, we can consider cystic fibrosis (CF), aspiration of stomach contents, immunodeficiency, tuberculosis, or congenital cardiopulmonary disease. Even though there is no evidence of intestinal malabsorption and no family history

of CF, CF should be considered in this patient and the patient should be screened with a sweat chloride test. In regards to aspiration of gastric contents, the patient has no signs or symptoms of coughing after eating or choking making this diagnosis less likely. Immunodeficiency can result in recurrent pneumonia as well. In humoral immunodeficiency, caused by decreased or absent immunoglobulins, clinical presentation can include sinus infections, ear infections, and pneumonia. This patient has no history of sinus infections or ear infections. Screening for humoral immunodeficiency should still be performed. Asthma can cause recurrent pneumonia usually in older children. This patient has no evidence of asthma based on pulmonary function tests that show a restrictive pattern and no reversibility with bronchodilators. Tuberculosis can be considered in this patient though the patient has no history of exposure or risk factors. Congenital defects of the heart and lung usually present with unilobar pneumonia or symptoms of heart failure. This patient had multilobar radiologic evidence of pneumonia and no evidence of heart failure. Further evaluation of cystic fibrosis, immunodeficiency, and tuberculosis should be considered.

Additional Workup

Sweat test, quantitative immunoglobulins, and PPD test were negative. High resolution CT scan of the chest demonstrated patchy areas of interstitial disease. Pulmonary endoscopy with biopsy was performed. Histological evaluation of the biopsy revealed a cellular interstitial infiltrate consisting mainly of lymphocytes, plasma cells, and macrophages in a bronchocentric pattern. No granulomas, vasculitis, or interstitial fibrosis were present. BAL also showed a $CD8^+$ T cell predominance.

Based on the biopsy and BAL fluid analysis results, the diagnosis of hypersensitivity pneumonitis was strongly considered. A home visit was performed to search for an etiologic antigen. The patient's home was noted to have a profound musty odor. The child's bedroom was damp to touch under the area of his bed. There was visible fungal growth underneath the carpet, on the linoleum, and on the wooden floor boards. Directly under the patient's room was an unventilated coal bin converted into a basement shower with a drain. There was extensive visible mold growth in the basement. *Penicillium* sp., *Aspergillus* sp., *Ulocladiup* sp., *Cladosporium* sp., and *Epicoccum nigrum* were identified by swab plate and open-air settled plates. Precipitating serum antibodies were found to *Epicoccum nigrum* in the patient's serum.

What Is Your Diagnosis and Why?

The patient's diagnosis was determined to be hypersensitivity pneumonitis due *to E. nigrum*. This diagnosis was difficult to determine based on the history obtained from the patient and family in regards to recurrent pneumonia. Lung biopsy results and BAL fluid analysis suggestive of HP resulted in a more detailed analysis of the patient's environment that helped elicit the significant mold that the patient was exposed to. The patient was started on a glucocorticoid taper and did not return to

his house. His physical exam demonstrated no rales, rhonchi, or wheezing. His ESR declined to 2 mm/h and pulmonary function tests returned to normal limits.

Discussion

The list of environmental agents that can cause hypersensitivity pneumonitis continues to increase. Due to the extensive list of antigens, it can be challenging to suspect hypersensitivity pneumonitis in patients. The primary exposures for the development of HP include occupational, agricultural, and those related to hobbies [2]. The allergenic particle needs to be small (3–5 μm) to reach the terminal airway. These antigens can be divided into bacterial, fungal, animal protein, and chemical sources. In the United States the most common cause of HP is avian related, hot tub lung, farmer's lung, and household mold exposure in order of prevalence.

The most common agricultural associated HP is Farmer's Lung due to thermophilic *Actinomycetes*. This bacteria thrives at temperatures of 70°C and grows in mold hay, compost, grains, silage, or mold sugarcane. Inhalation of metal-working fluids can result in Machine operator's lung due to antigens from *Pseudomonas* or *Acinetobacter*. Hot tub lung can be caused by inhalation of mycobacterium antigens.

Mold-contaminated material or water-damaged environments can result in a fungal cause of HP. Ventilation pneumonitis, is due to contaminated heating or cooling units that can aerosolize antigens from multiple fungi including *Cephalosporium*, *Curvularia*, and *Penicillium* [4]. This syndrome may also occur in patients exposed to small home humidifiers [2]. Malt worker's lung, Cheese worker's lung, and Mushroom picker's lung are all occupationally related fungal HP.

Pigeon breeders and bird fanciers have been recognized to develop HP due to animal proteins. A variety of birds can be implicated in causing HP. The antigen is from either the droppings or the blooms (a waxy substance that coats the feathers of birds) [4]. Other animals like rodents, oysters, or insects can serve as the antigen source for the development of Lab worker's lung, Oyster shell lung, or Wheat weevil disease, respectively.

Other antigens that can cause HP include chemicals like isocyanates and acid anhydrides found in paint and plastics. Inhaled heroin has been reported to cause HP [2]. Medications like nitrofurantoin, amiodarone, minocycline, and nadolol may cause pulmonary disease that resembles HP [2].

In diagnosing the etiology of HP, environmental history is essential. A detailed history of occupational exposures, hobbies, pets, water damage, and visible mold is very important. When HP is suspected and the environmental history is noncontributory, it is important to conduct a home visit. Antigenic sources, like the unventilated bathroom described in Case 2, can readily present themselves during a home visit, but may be overlooked by the patient and family during discussion of the environmental history. Samples can also be obtained during the home visit from cultures, swabs, or even ventilation dust. These samples can be sent to an experienced reference lab, along with the patient's serum, to determine the antigen and antibody precipitants and help in the diagnosis of the etiology of HP.

Questions

Case 1

1. The predictors of the diagnosis of HP include the following EXCEPT

   (a) Exposure to a known offending allergen
   (b) Weight loss
   (c) Recurrent episodes of symptoms
   (d) Wheezing

2. Acute HP is characterized by which of the following?

   (a) Flu like symptoms
   (b) Exertional dyspnea
   (c) Cyanosis
   (d) Weight loss

3. Evaluation of suspected HP includes the following studies EXCEPT

   (a) Chest x-ray
   (b) Complete blood count
   (c) Serum specific IgE
   (d) Serum antibody precipitants

4. In a classic presentation of acute HP, pulmonary function tests demonstrate

   (a) Restriction with low DLCO
   (b) Restriction with high DLCO
   (c) Obstruction with high DLCO
   (d) Restriction and obstruction with normal DLCO

5. Treatment of HP includes

   (a) Removing the patient from the offending antigen
   (b) Corticosteroids
   (c) Desensitization to the offending antigen
   (d) Both A and B
   (e) All of the above

Case 2

6. What is the approximate size of allergenic particles to reach the terminal airway?

   (a) 10–20 μm
   (b) 30–40 μm
   (c) 3–5 μm
   (d) 0.1–1 μm

7. The most common cause of agricultural associated HP is

   (a) *Acinetobacter*
   (b) *Actinomycetes*
   (c) *Penicillium*
   (d) *Cephalosporium*

8. What is the source of antigen in bird fancier's HP?

   (a) Bird Droppings
   (b) Bird Feathers
   (c) Bird Blooms
   (d) Both A and C
   (e) All of the above

9. What is the most common cause of HP in the United States?

   (a) Exposure to chemicals (e.g. acid anhydrides, isocyanates)
   (b) Avian related
   (c) Agricultural related (e.g. Farmer's Lung)
   (d) Household mold exposure

10. Bronchoalveolar lavage from HP patients is best characterized by an increase in

    (a) Eosinophils
    (b) Macrophages
    (c) Neutrophils
    (d) Lymphocytes

Answer key: 1. (d), 2. (a), 3. (c), 4. (a), 5. (d), 6. (c), 7. (b), 8. (d), 9. (b), 10. (d)

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Chapter 4
Pulmonary Eosinophilic Conundrums

Rokhsara Rafii, Nicholas J. Kenyon, and Samuel Louie

Abstract Pulmonary eosinophilic syndromes include a heterogeneous group of disorders. They have in common the presence of eosinophils in the airways and/or lung parenchyma. They may manifest peripheral eosinophilia and symptoms vary depending on what additional organs may be involved. The following cases highlight pulmonary eosinophilic syndromes as conundrums and emphasize a systematic approach to this heterogeneous group of disorders.

Keywords Acute eosinophilic pneumonia • Chronic eosinophilic pneumonia • Loeffler's syndrome • Pulmonary eosinophilic syndromes

Case 1

A 60-year-old man with a history of well-controlled asthma was transferred to the medical intensive care unit for increasing shortness of breath. The patient was initially admitted to the general medicine team with a chief complaint of increasing productive cough, subjective fevers, and increased dyspnea over the past 1 week. Six weeks prior to admission, the patient complained of a non-productive cough and was treated with doxycycline. His symptoms improved temporarily, prompting his return 3 weeks later. Upon admission, the patient also endorsed having nightsweats for the past 3–4 weeks, and a 16-pound weight loss over the past 3 months.

The patient has a history of obstructive sleep apnea for which he uses nightly CPAP, well-controlled asthma, type 2 diabetes, hypothyroidism, gout, and schizoaffective

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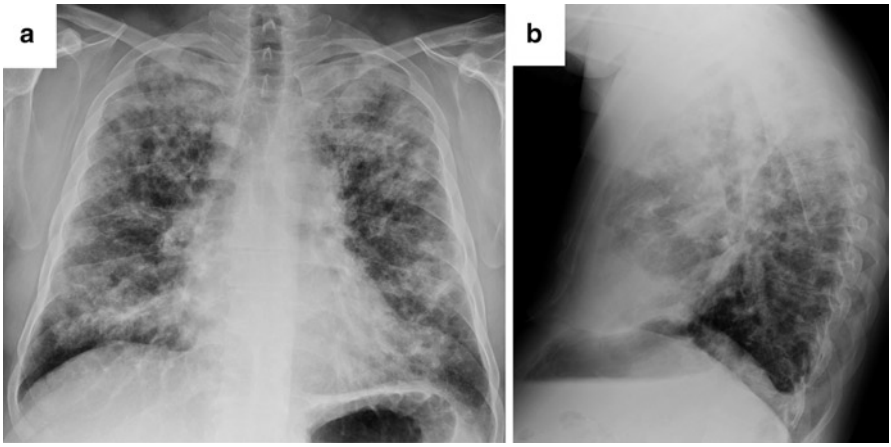

Fig. 4.1 (**a**) AP view of the chest on admission to the medical intensive care unit. Notable for increased opacities bilaterally with a peripheral predominance. (**b**) Lateral view of the chest on admission to the medical intensive care unit notable for diffuse opacities

disorder. He lives with his wife and two grandchildren who are 1 and 3 years of age. He has a 60 pack-year tobacco smoking history and quit cigarettes 10 years ago, occasionally smokes cigars (about 1/week), has no history of illicit drug abuse, and does not drink alcohol. He has two parakeets at home and cleans their cages daily. He worked in a resin plant for 1 year during his military service and thus had exposure to asbestos. He has no family history of any lung diseases or connective tissue disorders.

His list of medications includes citalopram 0.5 mg daily, abilify 20 mg daily, olanzapine 15 mg twice daily, risperidone 3 mg three times daily, diltiazem 360 mg SA daily, hydrochlorothiazide 37.5 mg daily, omeprazole 20 mg daily, indomethacin 75 mg daily, colchicines 0.6 mg daily, mometasone inhaler 220 mcg twice daily, and Combivent® inhaler four times daily. Review of systems was negative for hemoptysis, diarrhea, sinus congestion, and joint tenderness or erythema.

Physical examination revealed a slightly overweight man in respiratory distress with mild use of accessory muscles but able to answer questions appropriately. He had a temperature of 36.8°C, blood pressure of 121/68 mmHg, heart rate of 74 beats/min, a respiratory rate of 20–26 breaths/min, and an oxygen saturation of 92% on 2 L nasal cannula. No murmurs were appreciated on cardiac examination. Diffuse crackles (louder during the expiratory phase) were heard on lung auscultation, accompanied by an expiratory wheeze. His extremities were without clubbing, cyanosis, or edema and there was no rash on skin examination.

An arterial blood gas revealed a pH of 7.43, $PaCO_2$ of 57, and a PaO_2 of 64 on supplementation oxygen at 2 L/min by nasal cannula. Laboratory data was notable for an elevated WBC of 18.8 k/mm^3 with 2.1% peripheral eosinophils and 88% neutrophils. His serum bicarbonate was 24 mEq/L and his liver panel was unremarkable. His chest x-ray was abnormal with a predominance of diffuse bilateral airspace opacities, increased in both upper lung fields (Fig. 4.1). Over the next

5 days, the patient's breathing worsened though he maintained oxygen saturations greater than 90% on 6 L nasal cannula. Serial CBC was remarkable for increasing peripheral eosinophilia (maximum of 15%).

With the Presented Data, What Is Your Working Diagnosis?

The patient's history of asthma and exposure to young children requires consideration of an asthma exacerbation in the setting of a viral or bacterial respiratory infection. Other infectious causes such as active tuberculosis or atypical mycobacterial disease are possible given the patient's systemic symptoms. In addition, the patient lives with parakeets, which makes hypersensitivity pneumonitis a possibility. He is also prescribed an extensive list of medications including most recently an antibiotic, which make drug-induced eosinophilia an important consideration. The patient's weight loss and presence of nightsweats over the past several months bring hypereosinophilic syndromes and Churg–Strauss syndrome into consideration, and involvement of other organ systems would make these more likely candidates. Furthermore, Churg–Strauss syndrome, also known as "allergic angiitis granulomatosis," should be investigated in any patient with asthma and peripheral eosinophilia.

Differential Diagnosis

1. Hypersensitivity pneumonitis
2. Churg–Strauss syndrome
3. Acute eosinophilic pneumonia
4. Chronic eosinophilic pneumonia
5. Hypereosinophilic syndromes
6. Asthma exacerbation

Workup

Empiric, broad-spectrum antibiotic treatment was initiated given the acuity of this patient's presentation. A hypersensitivity panel, IgE level as well as ANCA testing was requested, and stool samples were sent to rule out the presence of ova and parasites. A computerized tomography (CT) of the chest was ordered to rule out cavitary lesions or possible abscesses not seen on chest x-rays. Furthermore, a fiberoptic bronchoscopy with a bronchoalveolar lavage (BAL) was performed to assess for possible pulmonary eosinophilia as well as to obtain specimens for culture.

The hypersensitivity panel was negative for bird antigen–antibody reactivity, IgE level was 278 IU/mL (reference range <100 IU/mL), and ANCA testing was negative. Multiple stool samples were negative for the presence of ova and parasites. Blood and sputum cultures were negative for bacterial and fungal infections,

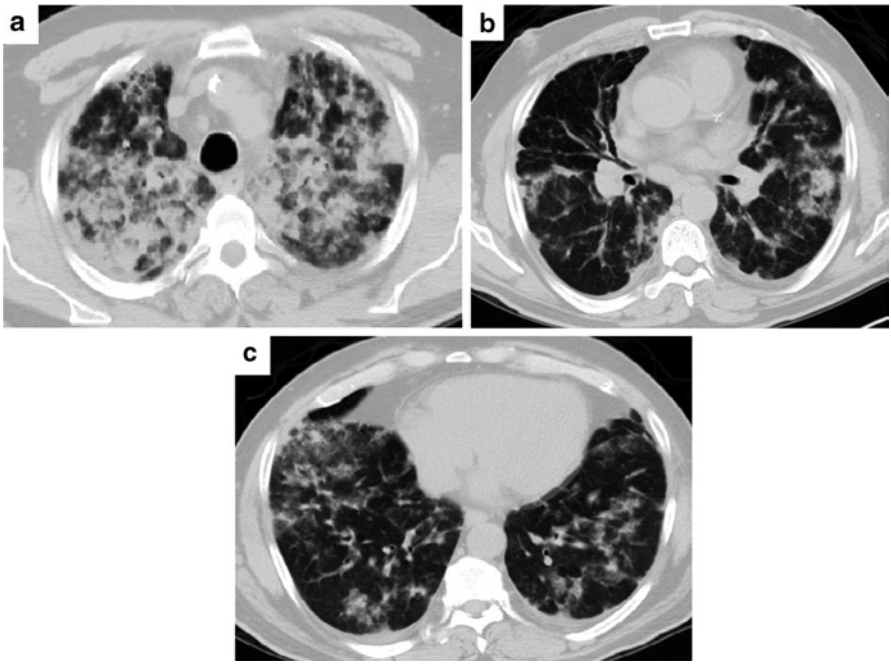

Fig. 4.2 CT chest, lung windows ((**a**) upper, (**b**) middle, (**c**) lower cuts) revealing multilobar opacities with a upper lobe predominance

and urine *Legionella* antigen was negative. Sputum was smear negative for acid-fast bacilli on three successive samples. A CT of the chest was notable for peribronchial consolidation and opacities in bilateral upper lobes and the right lower lobe, with moderate sparing of the left lower lobe (Fig. 4.2). Small bilateral pleural effusions were seen at the bases posteriorly. Small subcentimeter pre-tracheal and subcarinal lymph nodes were identified. A fiberoptic bronchoscopy was performed at the bedside, and BAL fluid consisted of a WBC of 1,300 k/mm^3 with 14% neutrophils, 24% lymphocytes, 1% monocytes, and 61% eosinophils. Transbronchial biopsies were negative for granulomas or evidence of vasculitis, but eosinophils were present.

What Is Your Diagnosis and Why?

Chronic Eosinophilic Pneumonia

The patient had no evidence of a vasculitis or multiorgan involvement, thus excluding Churg–Strauss and hypereosinophilic syndrome. Clinically, the patient had chronic symptoms (weight loss over the past 3 months and nightsweats, cough and dyspnea

over the past 3–4 weeks), thus excluding acute eosinophilic pneumonia. He also had alveolar infiltrates on his CXR that initially showed central sparing, and had >40% eosinophils on his BAL, a hallmark of chronic eosinophilic pneumonia.

Discussion

Pulmonary eosinophilic syndromes are characterized by an infiltrative lung disease with a predominance of eosinophils in any or all of the following: peripheral blood (normal <3% or absolute count <500/mm^3), sputum, BAL (normal <2%), and lung tissue [1, 2]. Pulmonary eosinophilic syndromes have been stratified in a variety of ways based on clinical, radiographic, and etiologic associations. Table 4.1 groups these pulmonary diseases into those of undetermined cause (idiopathic) such as acute eosinophilic pneumonia (AEP) and chronic eosinophilic pneumonia (CEP), Churg–Strauss syndrome, and hypereosinophilic syndromes, as well as those of determined

Table 4.1 Classification of pulmonary eosinophilic syndromes

Primary (idiopathic) pulmonary eosinophilic syndromes
- Acute eosinophilic pneumonia
- Chronic eosinophilic pneumonia
- Churg–Strauss syndrome
- Hypereosinophilic syndrome

Pulmonary eosinophilic syndromes of determined cause
- Allergic Bronchopulmonary Aspergillosis/Mycosis
- Infections
  - Parasitic
  - Non-parasitic (e.g. tuberculosis, fungal)
- Drug, toxin or radiation reaction
- Bronchocentric granulomatosis

Miscellaneous associations with possible eosinophlia

Lung diseases
- Organizing pneumonia
- Asthma
- Eosinophilic bronchitis
- Idiopathic interstitial pneumonias
- Langerhans cell histiocytosis
- Hypersensitivity pneumonitis

Malignancies
- Leukemia
- Lymphoma
- Lung cancer

Systemic diseases
- Sarcoidosis
- Rheumatoid arthritis
- Sjogren's syndrome

cause (secondary) eosinophilic pneumonias due to parasitic infections, drug, toxin or radiation-induced reactions, allergic bronchopulmonary aspergillosis (ABPA) and bronchocentric granulomatosis. A third category encompasses a miscellaneous group of conditions that are associated with eosinophilia, such as asthma, organizing pneumonia, hypersensitivity pneumonitis, neoplasms, as well as systemic diseases such as rheumatoid arthritis and sarcoidosis (Table 4.1) [1, 2].

Thorough history and physical examination is crucial in the workup of pulmonary eosinophilic syndromes. The clinical picture is dictated by which organs are infiltrated by eosinophils. This can range from general malaise to fever, shortness of breath, difficult-to-control asthma, or extrapulmonary findings such as a skin rash, rhinosinusitis and heart failure. Information regarding time of onset, duration of symptoms, and precipitating factors such as inhalation of dust are important clues. In addition, a review of new and old medications, occupational and environmental exposures, and travel history are vital in discovering the etiology if not specific kind of eosinophilic pneumonias [2].

Characteristic clinical and radiological features in conjunction with the presence and degree of alveolar or serum eosinophilia are necessary to diagnose pulmonary eosinophilic syndromes. To that end, laboratory data including measurement of peripheral serum eosinophils, cultures, serum IgE levels, spirometry, and radiographic imaging (such as a chest x-ray and computerized tomography) are important adjuncts. A preliminary diagnosis of a pulmonary eosinophilic syndrome should be made if clinical, laboratory and radiographic findings are present.

It is important at this point of the workup to seek out distinguishing clues. For example, the presence of asthma, as in this patient, would narrow down the possibilities to the idiopathic "ABC" eosinophilic disorders – AEP, bronchocentric granulomatosis, Churg–Strauss syndrome and CEP. Elevated IgE levels (>1,000 IU/mL) and asthma symptoms should suggest ABPA, hypereosinophilic syndrome, Loeffler's syndrome and Churg–Strauss syndrome.

Finally, the use of BAL fluid has markedly reduced the need for a lung biopsy. Both video-assisted thoracic surgery (VATS) and transbronchial biopsies are thus reserved for more difficult to diagnose cases, when tissue confirmation is required in confusing cases or to rule out lung cancer and infection before adding cytotoxic drug regimens to systemic corticosteroids [1].

Based on the duration of symptoms and particularly the markedly elevated eosinophils in his BAL, this patient was diagnosed with CEP. CEP consists of respiratory and systemic symptoms that progress over weeks to months [1]. Symptoms can consist of cough, dyspnea, chest pain, weight loss, fatigue, and nightsweats. There is a female predilection with a 2:1 ratio, and the peak incidence occurs in the fifth decade of life, though the age span for this disease ranges from 18 to 80 years [3]. Two-thirds of patients also have asthma, as was the case with our patient. However, neither asthma nor a history of atopy is a prerequisite for CEP.

While the cause of CEP is enigmatic, it is thought that an unknown insult or stimulus leads to an accumulation of eosinophils in the lungs, and these eosinophilic infiltrates predominate on histopathologic examination [4]. The absence of intraluminal organization of the alveolar filling in the distal airspaces differentiates CEP from cryptogenic organizing pneumonia. Interleukin-5 (IL-5), a cytokine that

recruits eosinophils from the bone marrow, plays an important role in the development of CEP [4]. The concentrations of IL-5 as well as other eosinophil-active cytokines such as IL-6 and IL-10 are increased in BAL specimens from patients with CEP. Mepolizumab, an anti-IL-5 antibody, may decrease steroid dosing and improve the care of some patients with hypereosinophilic syndromes, particularly those patients that are negative for the FIP1L1-PDGFRA gene [3].

Imaging for CEP classically reveals peripheral, often bilateral, alveolar opacities, and has been described as the "photographic-negative of pulmonary edema" on chest radiographs [1]. The relative central sparing can be appreciated in this patient's frontal radiograph in Fig. 4.1a. The density of the opacifications can range from ground-glass opacities to dense lung consolidation, and can be migratory [1, 4]. Pulmonary hemorrhage cannot be entirely excluded even in the absence of hemoptysis. Acute pneumonia (viral, bacterial, or fungal) should always remain a concern until infection has been excluded with confidence.

The majority of patients with CEP have peripheral eosinophilia, with mean eosinophil cell counts of >30% of the total blood leukocyte count [2]. C-reactive protein and erythrocyte sedimentation rate are typically elevated, and serum IgE is increased in about half of the cases. The hallmark of CEP, however, is the significant eosinophilia in the BAL fluid, usually >40% [1]. Only hypereosinophilic syndromes or "eosinophilic leukemia" is known to have BAL eosinophilia that can reach higher values, at times >70%.

Pulmonary function tests can be normal in one-third of the patients with CEP, though one-third to one-half of patients can have either obstructive or restrictive defects [1, 4]. Treatment of CEP with corticosteroids typically reverses the abnormalities, though obstructive findings may persist in some.

The standard therapy for CEP is systemic corticosteroids. A rapid response to treatment both symptomatically (within 48 h in 80% of patients) as well as radiographically (within 1 week in 70% of patients) is characteristic of CEP [1]. The recommended initial dose is 0.5 mg/kg/day of oral prednisone for 2 weeks with a gradual taper. There is no proven protocol and every taper must be individualized over months to 1 year or longer. Though typically described as having a good prognosis once treated, the rate of relapse is high and may require re-dosing of corticosteroids and, in some patients, prolonged maintenance doses for disease control. In addition to managing symptoms of the eosinophilic disorder as well as the side-effects of corticosteroids, spirometry should be performed during follow-up since airway obstruction may occur in the absence of other findings [4].

Given the severity of his symptoms, this patient was treated with methylprednisone 1 g/day for 3 days, then 1 mg/kg of prednisone with a gradual taper. His symptoms and radiographic abnormalities improved within the first 3–5 days of treatment initiation and follow-up: (Figs. 4.3 and 4.4). However, his disease has proven to be very steroid dependent, and he has required treatment doses of 15–30 mg daily of prednisone during the first year after diagnosis. The patient also removed the parakeets from his home shortly after diagnosis to eliminate any possible additional aeroallergens. Unfortunately, our patient increased not only his number of cigars to daily but also restarted smoking cigarettes on a daily basis. Thus, controlling both his asthma and CEP has proven to be difficult, albeit on an outpatient basis.

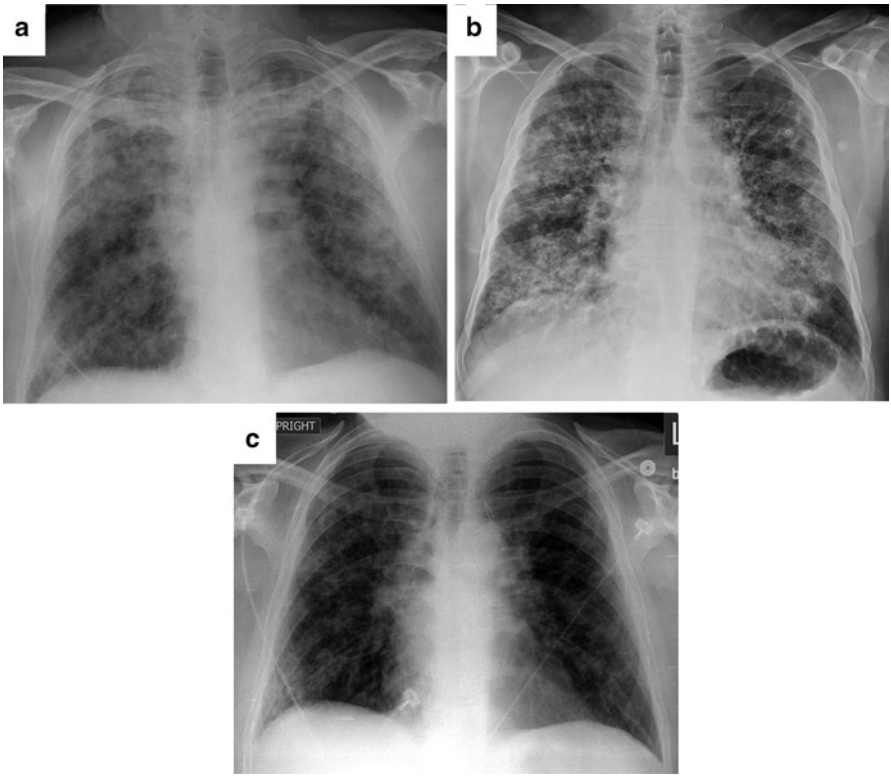

Fig. 4.3 AP views of the chest during hospitalization (**a**) Hospital day 6: progression of opacities with alveolar filling diffusely, pre-treatment with corticosteroids. (**b**) Hospital day 10: 3 days after initiation of corticosteroid therapy. Note a decrease in the multilobar opacities. (**c**) Hospital day 11: 4 days after initiation of corticosteroid therapy, with continued radiographic improvement

It is important to note several key differences between CEP and AEP. AEP presents in a much more acute fashion, typically with radiographic findings of diffuse bilateral pulmonary infiltrates often mistaken for acute lung injury or acute respiratory distress syndrome, and the patient typically requires mechanical ventilation [2]. In further contrast to CEP, AEP has a male predominance and patients do not typically have a history of asthma. Symptoms include cough, dyspnea, malaise, myalgias, nightsweats of less than 1 month's duration, and physical findings include fevers, rales, rhonchi and hypoxemia. A BAL with >25% eosinophils is one of the diagnostic findings of AEP in the absence of known drugs or infections that can cause the same. AEP is also notable for the absence of peripheral eosinophilia initially (though this can be seen within the next 3–4 weeks of disease onset). Patients with AEP respond quickly to corticosteroid therapy and have complete clinical and radiographic resolution without recurrence or residual of their illness within several weeks of therapy [2]. Table 4.2 outlines the diagnostic criteria for AEP and CEP and Table 4.3 compares the primary pulmonary eosinophilic syndromes.

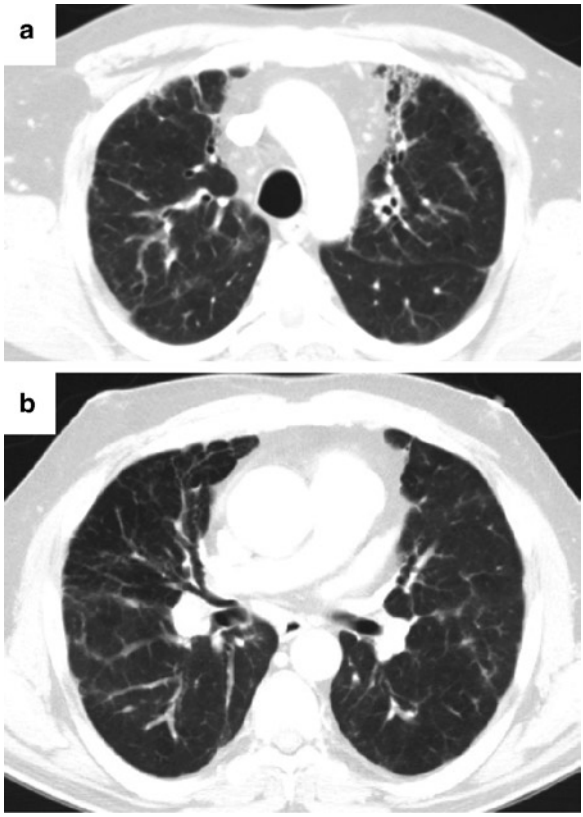

Fig. 4.4 CT chest, lung windows ((**a**) upper, (**b**) middle cuts): 2 month follow-up: notable for near-complete resolution of multilobar opacities

Table 4.2 Diagnostic criteria for AEP and CEP

Diagnostic criteria for AEP

1. Acute onset of febrile illness with respiratory manifestations (≤1 month duration)
2. Bilateral diffuse pulmonary infiltrates on chest radiograph
3. Hypoxemic respiratory insufficiency
4. Alveolar eosinophilia (BAL eosinophilia >25%)
5. Absence of known causes for pulmonary eosinophilia

Diagnostic criteria for CEP

1. Respiratory symptoms of ≥2 week duration
2. Alveolar eosinophilia (BAL eosinophils >40%)
3. Pulmonary infiltrates on chest radiograph typically with peripheral predominance
4. Absence of known causes for pulmonary eosinophilia

Table 4.3 Comparison of primary pulmonary eosinophilic syndromes

Test or imaging results	Acute eosinophilic pneumonia	Chronic eosinophilic pneumonia	Hypereosinophilic syndrome	Churg–Strauss syndrome
Blood eosinophilia (Normal <3% or absolute <500 mm^3)	None	High	Very high "eosinophilic leukemia"	High
BAL eosinophilia (Normal <2%)	>25%	>40%	>70%	>30%
CXR and/or chest CT	Bilateral alveolar opacities	Peripheral alveolar opacities	Bilateral alveolar opacities	Alveolar opacities
Total IgE > 100 IU/ml	Normal	Elevated in 67%	Elevated in 50%	High
Asthma history	None	50% (women > men)	None	100%
Signs and symptoms	Febrile illness ≤1 month Hypoxemia	Subacute illness (≥2 weeks)	Extrathoracic	Severe persistent asthma Extrathoracic

BAL, bronchoalveolar lavage

Case 2

A 74-year-old Mien-speaking woman was referred for consultation of difficult-to-control asthma. For the last 10 years, she suffered from recurrent episodes of shortness of breath, dyspnea on exertion, and at least three nocturnal awakenings per week secondary to a non-productive cough and occasional audible wheeze. Her activities of daily living were limited by dyspnea on exertion. She endorsed no known triggers, and denied a seasonal variation to her symptoms. In the past 1 year, she had two emergency room visits for presumed asthma exacerbations but was never hospitalized.

Her past medical history was significant for type-2 diabetes mellitus, gastroesophageal reflux, osteoporosis, and depression. Prior surgeries consisted of one cesarean-section. She had no family members with known asthma. She emigrated over 10 years prior from Laos and resided with her daughter and husband. She never smoked, though she endorsed second hand exposure to tobacco from her husband's smoking. She neither drank nor used illicit drugs. She had no pets. Review of systems was negative for gastrointestinal, cardiac, renal or hepatic diseases, but positive for a persistent pruritic skin rash on her upper and lower extremities. Her medications consisted of Duo-Neb® (ipratropium/albuterol nebulizer) treatment as needed, levalbuterol as needed (about four times daily), montelukast daily, loratadine, pulmicort respules twice daily, paroxetine 20 mg daily, novolog insulin 6 units pre-meal, lantus 10 units nightly, fosamax 70 mg weekly, calcium and vitamin D supplements.

On presentation, the patient's temperature was 99°F, and her blood pressure was 131/70 mmHg, heart rate was 99 beats/min, and her respiratory rate was 18 breaths/min. Her oxygen saturation was 90% on ambient air. She had no oral thrush and no sinus tenderness on palpation. There was no palpable lymphadenopathy in the cervical, supraclavicular or axillary chains. She had a diffuse wheeze bilaterally on lung auscultation. Her heart had a regular rate and rhythm and was without murmurs. No peripheral edema, clubbing or cyanosis was seen on her extremities. She had a skin rash on the upper and lower extremities bilaterally which consisted of pink circumscribed lesions that were non-blanching, and some excoriations were noted (Fig. 4.5). She had no focal neurological abnormalities.

Her CBC was notable for a microcytic anemia (hemoglobin 9.1 g/mm^3, MCV 60%) and peripheral eosinophils of 4.7% (0.4 k/mm^3). Her chemistry panel was unremarkable. An IgE level drawn 1 year prior was 4,010 IU/mL. Her liver panel was unremarkable. Office spirometry was notable for a reduced FEV1 (0.72 L, 48% of predicted), FVC (0.84, 44% predicted), and an FEV1/FVC ratio of 86%. Chest x-ray was remarkable for the presence of a left lingular alveolar density without pleural effusions (Fig. 4.6). A CT chest performed 2 years prior revealed mediastinal lymphadenopathy and bilateral atelectasis.

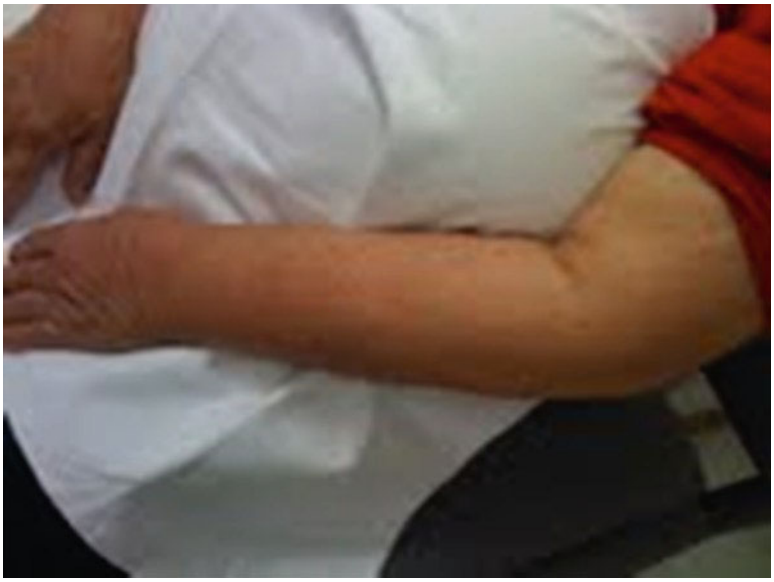

Fig. 4.5 Left arm: notable for a maculopapular skin rash

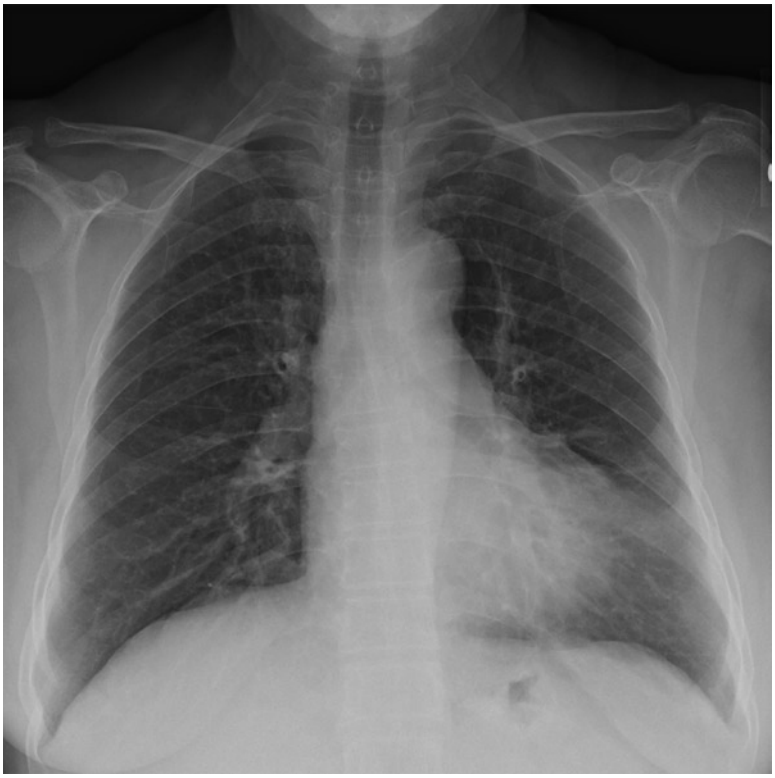

Fig. 4.6 PA view of the chest: remarkable for lingular opacity

With the Presented Data, What Is Your Working Diagnosis?

This patient has severe persistent asthma that is poorly controlled, requiring corticosteroids and frequent medical attention for acute exacerbations. However, she also has several other signs and symptoms that warrant further investigation of the etiology of her worsening condition. The syndrome of asthma, pruritic rash, infiltrates on imaging, and an elevated IgE prompt workup of Churg–Strauss syndrome, ABPA, and parasitic infections.

Differential Diagnosis

1. Churg–Strauss syndrome
2. Allergic bronchopulmonary aspergillosis
3. Loeffler's syndrome
4. Severe persistent asthma

Workup

As part of an assessment for allergies as well as ABPA, a radioallergosorbent test (RAST) against aeroallergens should be performed, and the presence for IgG and IgE precipitin for *Aspergillus species* should be assessed. Also, testing the stool for ova and parasite should be included in the workup for all patients with peripheral eosinophilia. One may also consider performing a skin biopsy to further evaluate her rash and the possibility that this may be part of a vasculitis.

The patient's RAST panel was negative for aeroallergens and serum precipitins were negative against *Aspergillus fumigatus*. A repeat IGE level was again elevated at 2,137 IU/mL. Her stool ova and parasite test was remarkable on multiple specimens for larvae resembling *Strongyloides stercoralis*.

What Is Your Diagnosis and Why?

Strongyloides stercoralis with Loeffler's Syndrome

While the patient's asthma was poorly controlled, her adherence to the use of bronchodilators, inhaled corticosteroids, oral corticosteroids and repeat acute exacerbations indicate that an alternative diagnosis should be pursued. Although an IgE level >1,000 IU/mL warrants consideration of ABPA, her serum precipitins were negative for *Aspergillus fumigatus*. Furthermore, the patient's skin

rash prompts evaluation for a vasculitis with consideration of Churg–Strauss syndrome. However, this patient's stool ova and parasite testing was diagnostic for *Strongyloides stercoralis*.

Discussion

Parasitic eosinophilic pneumonias are the most common cause of eosinophilic pneumonias worldwide [1]. Clinical findings are typically non-specific, and clinicians must maintain a high index of suspicion in order to make this diagnosis in a timely fashion. The more common parasitic infections are caused by *Wuchereria bancrofti* and *Brugia malayi*, *Ascaris lumbricoides*, *Toxocara canis*, and *Strongyloides stercoralis*.

Tropical pulmonary eosinophilia is due to the filarial parasites *Wuchereria bancrofti* and *Brugia malayi*. Larvae are deposited by mosquitoes on human skin, which then enter into the bloodstream and develop into mature worms that reside in lymphatic vessels [1]. Symptoms consist mostly of cough, which may be accompanied by fever, weight loss and anorexia. Chest radiograph shows multiple bilateral opacities, and there is marked alveolar eosinophilia on BAL. The diagnosis is made by a strongly positive serology in patients residing in an endemic area who have persistent blood eosinophilia and elevated IgE levels. Clinical improvement is seen within weeks of initiating therapy with diethylcarbamazine.

Ascaris lumbricoides is the most common helminth that infects humans. It is more commonly seen in tropical and subtropical regions [1]. It is transmitted through food that is contaminated by human feces containing parasitic eggs. Loffler's syndrome can be evident during the migration of the larvae through the lung. Symptoms include cough, wheezing, transient fever, and pruritic lesions, and blood eosinophilia is also present.

Visceral larva migrans syndrome is caused by *Toxocara canis*, and can occur worldwide. Children are at highest risk of infestation by ingesting the eggs released by female worms in the feces of infected dogs, typically through oral ingestion of soil from public playgrounds [1]. Most hosts remain asymptomatic, while others can suffer from fevers, seizures, cough, dyspnea and wheeze, and pulmonary infiltrates on chest radiographs. Eosinophils are elevated both in the blood as well as on BAL.

Strongyloides stercoralis, present in this patient, is an intestinal nematode found in temperate regions of the United States (southern Appalachian region including eastern Tennessee, Kentucky and West Virginia), tropics and subtropics, and in Africa, the West Indies, Southeast Asia, South America, Bangladesh and Pakistan [5]. Approximately 55–100 million people are infected worldwide. Infected immigrants to the United States are often misdiagnosed for an average of 5 years, particularly when they reside in non-endemic areas [5].

The life cycle of *Strongyloides* is more complex than that of other parasites, and consists of a free-living cycle and a parasitic cycle. As part of the parasitic cycle, the filariform larvae in the soil penetrate intact skin and infect the human host.

The larvae then enter the bloodstream and are transported to the lungs, where they penetrate the alveolar space [6]. The larvae then ascend the airways and trigger the host to cough, at which point they are swallowed and arrive into the gut. Once embedded into the intestinal mucosa, they reproduce asexually and lay eggs that hatch into rhabditiform larvae. The larvae then migrate into the intestinal lumen, and either leave the host through feces or mature into filariform larvae that infect the intestinal mucosa or skin of the perianal region and restart the parasitic cycle. This form of autoinfection can result in the persistence of infection for decades. If the rhabditoform larvae leave the host via feces, it can either mature into infectious filariform larvae or enter the free-living cycle.

Given the various stages in the parasite's life cycle, clinical manifestations of the infection are multiform, and include Loeffler's syndrome (presence of pulmonary infiltrates), chronic intestinal infection, asymptomatic autoinfection, and dissemination in the form of hyperinfection syndrome [6]. In the immunocompetent host, chronic and symptomatic infections may include abdominal discomfort, bloating, nausea, vomiting, diarrhea and anorexia, as well as respiratory complaints such as cough, dyspnea, and wheeze. Some individuals may develop a maculopapular or urticarial serpiginous rash called larva currens, pathognomonic for *Strongyloides* infection [5]. Fluctuating eosinophilia is present in about 75% of infected individual patients.

Autoinfection can result in the most life-threatening forms of the disease, hyperinfection syndrome (an increase in the worm burden) and dissemination (spread of the parasite to other organs) [5]. Clinical findings associated with hyperinfection vary from fever, chills, paralytic ileus, ulcerative enteritis, acute respiratory distress syndrome that may require mechanical ventilation, as well as alveolar hemorrhage. In the immunosuppressed patient, peripheral eosinophilia may be absent, which portends to a poorer prognosis. With dissemination, the patient may develop bacteremia, meningitis, and gram-negative sepsis.

Risk factors for hyperinfection syndrome and dissemination of the parasite include any form of immunosuppression such as immunosuppressive therapies including corticosteroids, human T-lymphotropic virus-1 (HTLV-1) infection, solid organ transplantation, hematologic malignancies, hypogammaglobulinemia, chronic alcohol consumption, uremia, severe malnutrition, and diabetes mellitus [5].

The diagnosis of *Strongyloides* includes stool testing for the larvae. Detection of the larvae from a single stool sample is only 25%, and multiple specimens (three are recommended) must be obtained for this reason. A complete blood cell count should be obtained to check for peripheral eosinophilia (again, this may be absent in the immunosuppressed patient). Those with respiratory symptoms should have their sputum samples evaluated for the parasite.

Strongyloides infection is treated with ivermectin, thiabendazole, or albendazole. Ivermectin is better tolerated and is the standard of care at 200 mcg/kg once daily for 2 days [5]. The cure rate is 94–100% [6]. Follow-up stool tests should be performed over a 3-month period to determine that the infection was successfully treated. Serology titers and peripheral eosinophilia should also decrease. For hyperinfection and disseminated disease, ivermectin is administered until symptoms resolve and stool tests become negative for 2 consecutive weeks.

Diagnostic workup for our patient was notable for two out of three stool specimens being positive for the presence of *Strongyloides* larvae. Serology was also notable for significantly elevated IgG antibody against the threadworm. She was treated with albendazole and on follow-up, her rash had improved, but her asthma was still poorly controlled. Three consecutive stool samples obtained 6 months later were negative for the larvae. Serum IgG antibody against the parasite was also decreased on follow-up. However, given that her rash had not resolved completely and her asthma was still poorly controlled, she was prescribed a second round of treatment with albendazole, after which her rash resolved, and her asthma management improved significantly.

Questions

1. What is the gender predominance with CEP?

   (a) Male
   (b) Female

2. What are the lowest accepted cutoffs for alveolar eosinophilia (obtained on BAL) for CEP?

   (a) >10%
   (b) >25%
   (c) >40%
   (d) >75%

3. Which form of eosinophilic pneumonia typically has radiographic evidence of infiltrates with peripheral predominance?

   (a) AEP
   (b) ABPA
   (c) CEP
   (d) Parasitic eosinophilic pneumonia

4. How does AEP differ from CEP with regard to response to treatment and follow-up?

   (a) Unlike CEP, AEP has a slow response to treatment but rarely recurs
   (b) Unlike CEP, AEP has a slow response to treatment and frequently recurs
   (c) Unlike CEP, AEP has a rapid response to treatment and rarely recurs
   (d) Unlike CEP, AEP has a rapid response to treatment but frequently recurs

5. What role do transbronchial biopsies play in the diagnosis of eosinophilic pneumonias?

   (a) They are essential in the diagnosis of eosinophilic pneumonias
   (b) They have replaced the need for a VATS-guided lung biopsy
   (c) They can be used interchangeably with BAL fluid
   (d) They are deemed necessary only in difficult to diagnose cases

6. What is the most common cause of eosinophilic pneumonias worldwide?

   (a) Parasitic eosinophilic pneumonias
   (b) ABPA
   (c) Drug-induced eosinophilic pneumonias
   (d) Asthma-associated eosinophilic pneumonias

7. Describe the mechanism for autoinfection with *Strongyloides stercoralis*?

   (a) Filariform larvae in the soil penetrate intact skin and infect the human host
   (b) Once embedded into the intestinal mucosa, they reproduce asexually and lay eggs that hatch into rhabditiform larvae
   (c) The larvae ascend the airways and trigger the host to cough, at which point they are swallowed and arrive into the gut
   (d) The larvae migrate into the intestinal lumen and mature into filariform larvae that infect the intestinal mucosa or skin of the perianal region and restart the parasitic cycle

8. What percentage of persons with chronic *Strongyloides* are asymptomatic?

   (a) <15%
   (b) <25%
   (c) >50%
   (d) >75%

9. While there is no gold standard for diagnosis, how is the diagnosis of *Strongyloides* typically made?

   (a) Testing a minimum of three stool samples for larvae
   (b) It is a diagnosis of exclusion and proper history and physical examination are imperative
   (c) Peripheral eosinophilia and at least two stool samples tested for larvae
   (d) Peripheral eosinophilia and the presence of respiratory symptoms

10. What are the risk factors for developing hyperinfection?

    (a) Host immunosuppression
    (b) Residence in an endemic region
    (c) Ingesting contaminated foods
    (d) Being younger than 18 years of age

Answer key: 1. (b), 2. (c), 3. (c), 4. (c), 5. (d), 6. (a), 7. (d), 8. (c), 9. (a), 10. (a)

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Part II
Occupational Lung Diseases

Chapter 5
Occupational Asthma to Low and High Molecular Weight Agents

Jonathan A. Bernstein

Abstract Occupational asthma is responsible for up to 15% of all causes of asthma. In this chapter, two very different causes of occupational asthma, one secondary to a low molecular weight chemical and one due to a high molecular weight protein, but both with very similar evaluation and management scenarios are presented. These instructional cases should permit the reader to determine how to approach suspected occupational asthma cases in the clinical setting.

Keywords Occupational asthma • Trimellitic acid anhydride • Enzymes • Lactase • Asthma • Asthma treatment • Bronchoprovocation • Low molecular weight chemicals

Case 1

A 42-year-old Hispanic male presents with increasing shortness of breath, chest tightness and wheezing which began approximately 9 months before his visit. These symptoms developed gradually over time; initially they were intermittent but now occur continuously on a daily basis. He has no history of allergic rhinitis, eczema or asthma. His past medical history is remarkable for high cholesterol which is diet controlled, but otherwise he is healthy. He has no past surgical history, does not drink alcohol or smoke cigarettes and has no family history of asthma or allergies. Of note, he noticed his symptoms were preceded by a runny nose at work. His work history is remarkable for working as a packaging operator in a warehouse for a large

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chemical manufacturing company for the past 2 years. He reports that he is exposed to several chemicals including maleic anhydride, trimellitic anhydride and phthalic anhydride. He is required to wear a respirator while working with these chemicals but often is non-adherent as it makes it difficult for him to breath. Prior to working at the chemical plant, he worked as a landscaper and in construction but never experienced any respiratory symptoms during this time. He notices his symptoms significantly improve on weekends and during vacation. During his initial evaluation, his physical examination was normal.

Clinical Evaluation

An asthma control test (ACT) score was 9. A peak expiratory flow rate was 320 L/min (predicted 690 L/min for his age and height). Subsequent spirometry revealed an FEV1 2.4 L (48% predicted) which improved to 3.5 L (85% predicted) after bronchodilators (46% change). His FEF25-75 was 1.6 L/s (35% predicted) and improved to 3.6 L/s (70% predicted) after bronchodilators. An exhaled nitric oxide level was 72 ppb.

What Additional Tests/Information Is Required?

Chest x-ray
Material data safety sheets
Allergy Skin testing to assess atopic status

Initial Impression

Occupational asthma secondary to acid anhydrides
Work-aggravated asthma
Irritant-induced asthma

What Treatment Recommendations Should Be Made?

Treat with oral prednisone 40 mg qd for 5 days and taper by 5 mg every 2 days
Start a combination ICS and LABA
Rescue SABA
Instruct on inhaler technique
Monitor PEFR in and out of the workplace for 2 weeks
Follow-up visit in 2 weeks

Follow-Up Visit 2 Weeks Later

On return visit the worker is feeling much better but still has intermittent chest tightness and has to use his rescue inhaler twice during the day during work and at night at least 3–4 times a week. His chest x-ray showed some mild hyperinflation but was otherwise unremarkable. Review of material data safety sheets confirmed that he was exposed primarily to trimellitic anhydride (TMA). Review of the 2-week peak flow diary for variability indicated greater than 20% variability from morning to evening 8 out of 14 days. Allergy skin testing during his visit revealed a positive skin prick test to dust mites and cockroach only. Repeat spirometry revealed his FEV1 improved to 3.2 L (80% predicted); however his ACT was still 16 indicating his asthma was still not well controlled.

Recommendations

Taper off prednisone as instructed
Continue controller therapy and SABA as needed
Remove from further exposure to TMA
Obtain specific IgE antibody levels to TMA and/or skin test to TMA to identify specific IgE response
Follow-up in 4 weeks

Four Week Follow-Up Visit

On return visit the worker is feeling much better. He was reassigned to a different warehouse where there was no TMA exposure. His ACT score was 21 and he was not having nocturnal symptoms, compromise in his daily activities or having to use a daily SABA inhaler. Serum-specific IgE antibody to TMA was positive by immunocap assay confirming TMA sensitization. Repeat spirometry revealed an FEV1 of 4.2 L (98% predicted) and FEF25-75 of 4.5 L/s (95% predicted). The worker was recommended to continue controller therapy, avoidance of TMA and follow-up in 3 months for monitoring of asthma control over time.

Final Diagnosis: TMA-Induced Occupational Asthma

Discussion

Trimellitic anhydride (TMA) is an acid anhydride that is widely used as a curing or hardening agent in epoxy resins; in the production of plasticizers for polyvinyl chloride; and in polyester and alkyd resins [1]. The National Institute of

Occupational, Safety and Health (NIOSH) estimate that 20,000 workers in the United States have developed TMA-induced occupational illness in various work processes [2]. Because it is a solid, manufactured as white flakes, with a low vapor pressure below 1.1×10^{-7} mmHg, human exposure to TMA can occur as a dust and/or as a fume. TMA can elicit symptoms in exposed individual as an irritant after exposure to TMA or its hydrolyzed product, trimellitic acid (TMLA) through inhalation and dermal routes causing respiratory symptoms and skin rashes, respectively [3]. Trimellitic anhydride can cause a spectrum of respiratory hypersensitivity reactions in humans with well-defined immunological mechanisms, which are manifested as four immunological syndromes (Table 5.1) [4]. The immunological effects in the lung are the result of TMA acting as a hapten that can react with the body's own proteins to form trimellityl (TMA)-protein conjugates [5]. Specific antibodies against TMA-modified proteins are directed primarily against new antigenic determinants that arise from these interactions between TMA and self-proteins, such as human serum albumin [5]. With re-exposure to TMA, individuals who have produced specific antibodies against TMA or TMA-modified proteins may experience one or more of the immunological syndromes. The most common immunologic clinical conditions described for TMA-IgE sensitized workers have been rhinitis and asthma [4]. Once sensitized, symptoms can occur within minutes after TMA re-exposure. However, workers can also exhibit a latency period of weeks to years prior to the onset of symptoms. Typically, reports of rhinitis and/or conjunctivitis precede the occurrence of asthma symptoms [6]. In a cross-sectional study conducted at a TMA-manufacturing plant with 474 employees, nearly 7% ($n=32$) developed TMA-associated immune disorders consisting of asthma/rhinitis ($n=12$), active late respiratory systemic syndrome (LRSS) ($n=10$), LRSS in remission ($n=5$), late onset asthma ($n=4$) and late onset arthralgia ($n=1$) [4].

Diagnosis of occupational asthma requires a careful history inclusive of environmental exposures in and out of the workplace. Obtaining material safety data sheets can help identify agents the worker may be patient may be exposed to at work [7]. There are no conclusive clinical risk factors such as atopy, smoking, pre-existing airway hyperresponsiveness or HLA markers that predispose workers to the development of TMA-induced sensitization or progression to asthma [8]. Barker et al. demonstrated that a positive TMA skin test response was an independent risk factor for developing work-related bronchial hyperresponsiveness [9]. In this study, other factors such as smoking history, atopic status (i.e., sensitization to common inhalant allergens) and age were not significant after controlling for FEV1 [9].

The clinical evaluation should include a chest x-ray to exclude structural problems and pulmonary function testing to assess for airway obstruction. If improvement of FEV1 greater than 12% after bronchodilators is not observed and the patient's FEV1 is greater than 70% predicted, a methacholine challenge to assess for airway hyperresponsiveness should be performed. In order to establish work-related asthma, peak expiratory flow rate monitoring in and out of the workplace for 2–3 weeks can demonstrate peak flow variability greater than 20%, considered a significant change, which further supports a diagnosis of occupational asthma.

Table 5.1 Trimellitic acid anhydride clinical syndromes

Characteristics	Rhinitis/asthma	Late asthma	Late Respiratory Systemic Syndrome (LRSS) aka TMA flu	Pulmonary disease-anemia	Irritant-induced asthma
Latency period	Yes	Yes	Yes	Yes	No
Onset of symptoms after work exposure	Immediate (30–60 min)	4–12 h	4–12 h	Progressive with further work exposure	Variable depending on exposure
Clinical symptoms	Cough, wheeze, chest tightness, shortness of breath, rhinorrhea, nasal congestion, sneezing, post nasal drainage	Coughing, sneezing, tightness in chest, wheezing due to constriction of airways, sneezing, itching of nose	Resembles hypersensitivity pneumonitis. Coughing, wheezing and dyspnea often accompanied by malaise, chills, fever, muscle and joint pains	Hemoptysis, dyspnea, pulmonary infiltrates, restrictive lung disease, and anemia, as well as the same symptoms as LRSS.	Cough, chest tightness, wheezing, shortness of breath and upper airway and eye irritation, lacrimation, sneezing, and nasal discharge
Specific IgE	+	±	–	–	–
Specific IgG	+	±	±	±	–
Gell-Coombs Classification	IgE mediated	?Type I (late phase asthmatic response)	Type III (Immune-complex-mediated hypersensitivity)	Type II (Antibody-dependent cytotoxic hypersensitivity); Type III (Immune-complex-mediated hypersensitivity)	–

To determine whether a worker is sensitized to TMA, a serum-specific IgE immunocap antibody test can be performed which has good sensitivity and specificity for TMA sensitization. Trimellitic anhydride after conjugation with an exogenous protein like human serum albumin (HSA) is one of the few low molecular weight chemicals that can be used as a skin test reagent to assess for IgE-mediated sensitization. Although TMA skin testing has been found to correlate with the development of serum-specific IgE antibody responses and subsequent clinical disease, it does not correlate well to ambient TMA exposure concentrations indicating that the magnitude of exposure is not the critical factor for developing sensitization [9, 10]. Studies have found that there is good correlation between TMA skin testing and serum-specific IgE to TMA [11].

The gold standard for definitive diagnosis of occupational asthma induced by high or low molecular weight allergens is bronchoprovocation to the specific inciting agent. However, this diagnostic test needs to be done by experienced personnel in a controlled environment with emergency therapy readily available. Challenges to low molecular weight agents like TMA are particularly challenging, as they require more sophisticated equipment to monitor concentration, atmospheric pressure, temperature, humidity as well as changes in lung function and vital signs. For a number of reasons, specific bronchoprovocation is not routinely done in the United States which is in contrast to Canada where they are done routinely, as a positive challenge to an inciting agent is required before a worker is entitled to government compensation.

Once it is established that a worker is sensitized to TMA, the decision whether or not they should be removed from further TMA exposure has not been conclusively determined as not all sensitized workers develop clinical disease. The incidence of TMA illness and antibody levels has been demonstrated to decrease with lower exposures to TMA. Personal exposure levels below 0.002 mg/m^3 was successful in preventing workers from developing TMA illness or TMA-specific IgG antibodies [12]. However, there was still a 9% incidence of workers developing TMA-specific IgE antibodies among workers who didn't directly work with TMA or who didn't exhibit signs of TMA illness [12]. Other studies found no clear relationship between TMA exposure and the development of TMA illness [13]. Overall, the literature suggests variation and uncertainty in the dose–response relationship of TMA illness. The American Conference of Governmental Industrial Hygienists (ACGIH) and NIOSH have established a recommended exposure limit (REL) for TMA as 0.005 ppm in air (40 μg/m^3) as a time-weighted average for up to a 10-h workday and a 40-h workweek [3]. Currently, TMA manufacturers or companies that use TMA in their work process have implemented rigid environmental control measures in order to comply with these recommendations and minimize worker exposure. In one instance, a comprehensive immunosurveillance program to monitor TMA exposed workers for development of TMA sensitization and clinical disease has been established. This program has been very successful in identifying early detection of TMA sensitization and the development of upper and/or lowers respiratory symptoms so that the worker can be immediately removed from further exposure. In general, studies have found that the earlier workers are removed from further TMA exposure after developing respiratory symptoms the better their short- and long-term prognosis [13].

Follow-Up of Patient 6 Months Later

The worker was removed from further TMA exposure and continued to do well clinically. His ACT score was maintained at 25 and his lung function normalized. His TMA-specific IgE antibody test remained unchanged.

Case 2

A 38-year-old Caucasian female presents with rhinorrhea, nasal congestion and post-nasal drainage that has got progressively worse over the past 3 years. She has a history of physician diagnosed allergic rhinitis confirmed by skin testing as a teenager, which is worse during the spring and fall and around cats. Her current symptoms, however, seem to be present year round and appear to be worse at work compared to home. She is significantly better on weekends and vacation. She notes chest tightness and cough particularly when her rhinitis symptoms are most severe after a 12-h work shift. Here work history is remarkable for being employed in a pharmaceutical company where she blended and mixed different ingredients to be used for production of tablets. She notes that certain work areas were very dusty during peak batch runs of different agents. Her past history is remarkable for high cholesterol treated with simvastatin, and she uses a nasal corticosteroid as needed. She is otherwise very healthy. There is a family history of allergies on her mother's side. She does not smoke or drink alcohol. Her home environment is remarkable for one dog which she denies symptoms around. She has never been diagnosed with asthma.

Clinical Evaluation

Physical examination was normal. An asthma control test score was 22. A peak expiratory flow rate was 450 L/min (predicted 440 L/min for his age and height). Subsequent spirometry revealed an FEV1 3.7 L (98% predicted) which did not improve after bronchodilators. Her FEF25-75 was 4.0 L/s (101% predicted) and did not improve after bronchodilators. An exhaled nitric oxide level was increased at 40ppb (normal ≤20 ppb).

What Additional Tests/Information Are Required?

Chest x-ray
Material data safety sheets
Allergy Skin testing to assess atopic status
Methacholine challenge testing to assess for airway hyperresponsiveness

Initial Impression

Occupational asthma secondary to pharmaceutical agents?
Allergic work-aggravated asthma

What Further Evaluation/Treatment Recommendations Should Be Made?

Start a rescue short acting beta-agonist (SABA)
Instruct on inhaler technique
Monitor PEFR in and out of the workplace for 2 weeks
Schedule methacholine challenge test
Follow-up visit in 2 weeks

Follow-Up Visit 2 Weeks Later

Review of material data safety sheets confirmed that she was exposed to lactase (β-D galactosidase).During this visit the patient underwent skin prick testing to a panel of seasonal and perennial aeroallergens and was found to be sensitized to tree, grass and ragweed pollen in addition to cat and dust mites. Review of peak expiratory flow rate variability indicated several days over the past 2 weeks variability exceeded 20%. The chest x-ray was normal. A methacholine challenge revealed that the provocative concentration of methacholine that caused a 20% drop in FEV1 (PC_{20}) was 4.7 mg/mL (abnormal is ≤10 mg/mL).

Recommendations

Skin testing to lactase
Consider specific provocation sifting test to lactase to verify that lactase is the culprit
Continue SABA as needed
Remove from further exposure to lactase until testing is completed
Follow-up in 4 weeks

Four Week Follow-Up Visit

On return visit the worker is feeling much better. She was reassigned to a different warehouse where there was no lactase production. Her ACT score was 24, and she was not having nocturnal symptoms, compromise in her daily activities or having to use a daily SABA inhaler. A prick test to a 1: 1,000 dilution of lactase was positive

(wheat = 6 mm; flare = 26 mm). A specific provocation to lactase was deferred based on her clinical history of exposure, diagnosis of asthma, skin sensitization to lactase and improvement with avoidance of the workplace."

Final Diagnosis: Lactase Enzyme-Induced Occupational Asthma

Discussion

Enzymes are proteins that are used as biocatalysts to reduce/replace the use of chemicals in a variety of processes [14]. As catalysts, enzymes are used in a variety of industries including cleaning, food processing, animal feed, fuel alcohol, textile, paper and pharmaceuticals. In 1967, the first enzyme commercially introduced in the United States and England was "Alcalase®" which was derived from *Bacillus subtilis* through a submerged fermentation process for use in soap detergents [14]. Within 3 years, 80% of all soap detergents sold in the United States contained enzymes. Subsequently, Flindt and Pepys reported the first cases of respiratory symptoms in detergent workers after inhalation exposure to *Bacillus subtilis*-derived powdered enzymes, Alcalase and Maxatase® [15, 16]. Eighty percent of workers with respiratory symptoms elicited a apositive wheal and flare skin test response to skin test reagents prepared from the enzymatic material and *Bacillus subtilis* spore extracts [15]. These index cases demonstrated that enzymes were highly allergenic and that susceptible workers exposed to these agents were at increased risk for becoming sensitized and developing asthma.

Eventually, manufacturers who used enzymes in the work process implemented structural and procedural changes in the workplace to comply with the American Conference of Governmental Industrial Hygienists (ACGIH) recommendation of a threshold limit value (TLV) for subtilisin of 60 ng/m^3 [14]. These interventions included manufacturing equipment enclosures, improved work area exhaust ventilation systems, operational methods for safe handling of enzymes and novel enzyme coating methods to reduce enzyme friability and dust generation [14]. However, even with these preventive measures, workers were still observed to develop sensitization leading to the realization that an immunosurveillance program designed to closely monitor workers for enzyme sensitization and the development of respiratory symptoms was essential.

Cross-sectional and longitudinal studies have investigated potential risk factors for enzyme sensitization. Although most studies have found that atopic workers are more susceptible to becoming sensitized to enzymes, it is still unclear whether or not atopy is predictive of progression to clinical disease [14]. Although smoking was reported as a risk factor by two investigators, smoking, along with gender, race, age, HLA haplotypes have not been found to be consistent risk factors for enzyme sensitization [14, 17, 18].

In general, the immunopathogenesis of enzyme-induced sensitization is IgE mediated confirmed by enzyme-specific skin testing and/or serum-specific IgE

assays. In that enzymes are high molecular weight proteins, they can be used directly as skin test reagents. The development of IgE-mediated enzyme-induced occupational asthma has been confirmed by specific bronchoprovocation [14].

In general, enzymes are plant or microbial derived. Examples of plant-derived enzymes known to cause occupational sensitization and asthma include papain, widely used in cosmetic, food and pharmaceutical consumer products, chymopapain (a proteolytic enzyme, structurally related to papain) used for intradiscal dissolution of herniated lumbar discs, pepsin used as an additive in the production of liquors, cheeses and cereals and bromelain used in the pharmaceutical industry [14].

Microbial-derived enzymes are typically produced by bacterial microorganisms belonging to *Bacillus* sp. and *Pseudomonas* sp. and fungal organisms such as *Aspergillus* sp., *Streptomyces* sp. and *Trichoderma* sp. As mentioned above, the earliest and most common example of microbial- derived enzymes are those used in the manufacturing of soap detergents. These enzymes, which are serine proteases derived from several *Bacillus* organisms (also called subtilisins or subtilopeptidases), have been found to be useful in household cleaning agents because of their potent enzymatic activity which is stable over wide ranges of pH and temperature [14]. However, a number of microbial-derived enzymes have also been used in the food industry. For example, α-amylase enzymes derived from *Aspergillus oryzae* have been implicated in Baker's asthma. Investigators have reported that enzyme-induced sensitization and occupational allergy were highest in areas of bakeries with the highest exposure to these enzymes [19, 20]. Occupational asthma induced by cellulose and β-D-galactoside derived from *Aspergillus niger and oryzae* species, respectively, have been well documented in the pharmaceutical industry [21, 22]. A cross-sectional survey performed on 94 pharmaceutical workers exposed to *Aspergillus oryzae*- derived β-D-galactoside galactohydrolase revealed that 29% of exposed workers had lactase sensitization and lactase sensitized workers were nine times more likely to experience upper or lower respiratory symptoms compared to skin test negative subjects. Atopic workers were four times more likely to develop lactase sensitization compared to non-atopic workers. Reduction of lactase exposure and restricting atopic workers from working with lactase successfully prevented lactase-induced occupational symptoms [21]. Egg processing workers are typically at increased risk for developing occupational asthma induced by egg proteins such as ovalbumin, ovomucoid and conalbumin, but egg lysozyme sensitization has also been reported [14, 23]. A worker employed in a plant that manufactured hen egg white-derived lysozyme was previously reported to develop occupational asthma induced by inhaled egg lysozyme [23]. IgE-sensitization was confirmed by prick skin testing and serum-specific IgE antibodies to egg lysozyme and antigen specificity for egg lysozyme-specific IgE was confirmed by ELISA inhibition and bronchoprovocation to egg lysozyme [23]. Other examples of microbial-derived enzymes causing sensitization and occupational asthma include workers exposed to pectinases in the food industry, phytase and β-gluconase in the animal feed industry and porcine pancreatic amylase in a laboratory [14].

Evaluation of workers suspected for enzyme sensitization, begins with a comprehensive history including information regarding job description and work process, duration of exposure prior to onset of symptoms, temporal relationship between

symptoms and the workplace, description of the workplace, length of daily exposure and use of protective equipment such as clothing, gloves, and masks/respirators [14]. Material safety data sheets and industrial hygiene air sampling data identifying specific exposure(s) should be reviewed [7]. Allergy skin prick testing to indigenous seasonal and perennial allergens should be performed to assess for atopic status as this is a potential risk factor for enzyme sensitization. Skin prick testing to specific enzymes encountered in the workplace should also be performed. Enzyme extracts prepared for skin testing should first be administered to non-exposed control subjects using serial dilutions of the enzymatic extract to determine the least irritating concentration [14]. Peak flow monitoring at and away from work should be conducted to demonstrate peak flow variability related to workplace exposures. Spirometry before and after bronchodilators to demonstrate reversible airways disease consistent with asthma is essential. If spirometry is normal or reversibility cannot be demonstrated, then a methacholine challenge should be performed to confirm or exclude bronchial hyperresponsiveness, a central feature of asthma [14]. If the diagnosis of enzyme-induced occupational asthma is uncertain, then enzyme-specific bronchial provocation may be necessary. A standard technique described by Pepys is to have the subject transfer the enzyme powder back and forth between two trays in an enclosed room [14, 16]. The subject's FEV1 and forced vital capacity are measured at different time intervals during this sifting procedure to identify changes in lung function [16]. During these challenges, proper controls including a placebo challenge day should be included. The initial enzyme challenge concentration for provocation should be two- to threefold lower than the minimal concentration that elicits a positive skin test response. Bronchial challenges should only be performed by experienced personnel in a controlled setting with emergency therapy readily available [14, 16].

Once a diagnosis of enzyme-induced occupational asthma has been established, the treatment of choice is to remove the worker from further exposure. Treatment of a worker with enzyme-induced asthma is similar to the treatment of non-occupational asthma which requires regular use of an anti-inflammatory agent to reduce airway inflammation and the potential for airway remodeling and permanent airway obstruction [14]. The natural course for clinical improvement among workers with enzyme-induced occupational asthma is variable. However, the earlier symptomatic workers are identified in the course of their illness and removed from further exposure, the less likely they will be to suffer irreversible impairment due to airway obstruction [14]. It is not acceptable to treat with medications and allow a symptomatic worker to return to the same job or work area without reducing or eliminating exposure to the causative agent.

Follow-Up of Patient 6 Months Later

The worker was removed from further lactase exposure and continued to do well clinically. Her respiratory symptoms resolved and her ACT score was maintained at 25. A follow-up methacholine challenge test after removal from the workplace was negative. Re-skin testing to lactase was still positive.

Questions

1. All of the following statements are true except

   (a) Trimellitic acid is a respiratory irritant
   (b) TMA must first bind to an endogenous protein to become allergenic
   (c) The most common clinical condition caused by TMA is late respiratory systemic syndrome
   (d) TMA exposure occurs through the respiratory and dermal routes

2. Risk factors for TMA include

   (a) Smoking history
   (b) Atopy
   (c) Age
   (d) Race
   (e) None of the above

3. All of the following support a diagnosis of allergic TMA-induced asthma except

   (a) Positive skin test to TMA-HSA conjugate
   (b) Peak flow variability >20% in and out of the workplace
   (c) Positive methacholine challenge
   (d) Positive specific IgG antibody to TMA

4. All of the following statements are false except

   (a) Exposure levels below 0.002 mg/m^3 prevents the development of TMA-specific IgE
   (b) There is a clear dose–response exposure relationship for TMA illness
   (c) The recommended exposure limit (REL) for TMA is 0.005 ppm in air (40 μg/m^3)
   (d) Immunosurveillance programmes have been ineffective at preventing TMA-related illness

5. Which of the following statements is false:

   (a) Serum-specific IgE antibodies do not correlate well with TMA skin testing
   (b) The gold standard for diagnosis of TMA-induced asthma is specific bronchial challenge
   (c) Early removal from further TMA exposure after sensitization is recommended
   (d) TMA exposure does not correlate well with TMA sensitization

6. The following statements are true except

   (a) Enzymes are protein catalysts used in a number of different industries
   (b) The first occupational case of asthma induced by enzymes was in a detergent worker
   (c) Detergent enzymes are derived from *Bacillus subtilis*
   (d) Most detergents no longer contain enzymes due to the risk for sensitization

7. True statements about exposure to enzymes include all of the following except:

   (a) Enzymes are closely regulated by threshold limit value (TLV)
   (b) The TLV for subtilisin is 60 ng/m^3
   (c) Operational methods designed to reduce enzyme exposure in the workplace have been successful
   (d) Encapsulation or coating of enzymes is no longer performed

8. The most important risk factor for enzyme sensitization is:

   (a) Age
   (b) Gender
   (c) HLA haplotype
   (d) Atopy
   (e) Smoking

9. Applications for enzymes include

   (a) Meat processing
   (b) Baking
   (c) Detergents
   (d) Pharmaceuticals
   (e) All of the above

10. The most specific test for a diagnosis of enzyme-induced occupational asthma is

    (a) Positive skin test response to the enzyme
    (b) 12% improvement in FEV1 post bronchodilators
    (c) Specific provocation
    (d) Methacholine challenge

Answer key: 1. (c), 2. (e), 3. (d), 4. (c), 5. (a), 6. (d), 7. (d), 8. (d), 9. (e), 10. (c)

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Chapter 6
Malignant Pleural Mesothelioma

Tobias Peikert and James R. Jett

Abstract Malignant pleural mesothelioma (MPM) is an uncommon, almost universally lethal thoracic malignancy. It is closely associated with prior inhalational asbestos exposure. Despite some recent progress the diagnosis, staging and therapy of patients with MPM remain very difficult to the treating physicians. Herein we discuss some of these challenges based on the cases of two MPM patients.

Keywords Pleural thickening • Asbestos • Pleural effusion • Mediastinal lymphadenopathy • Malignant pleural mesothelioma • Spontaneous pneumothorax • Endobronchial ultrasounds guided biopsy

Case 1

An 80-year-old woman was in her usual state of health until she developed progressive dyspnea and non-productive cough a month prior to her initial evaluation. She was a lifetime non-smoker and retired bank employee. Her chest radiograph at presentation revealed a new right-sided hydropneumothorax (Fig. 6.1).

The patient had no previously diagnosed lung diseases. Specifically, she had no history of asthma, chronic obstructive pulmonary disease, emphysema, prior pneumothorax, tuberculosis or other lung infections. She denied any HIV risk factors

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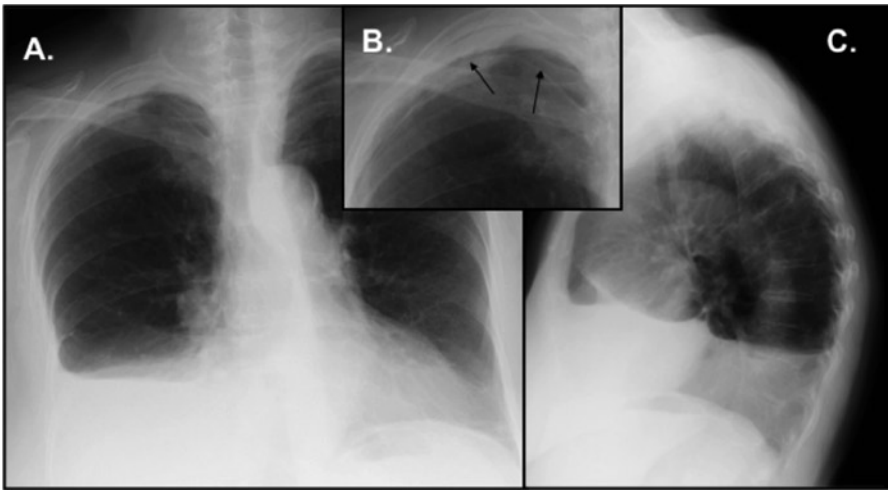

Fig. 6.1 Anterior-posterior (**a**) and lateral (**c**) Chest radiograph demonstrates a right-sided hydropneumothorax. The *black arrows* indicate the pneumothorax in the right apex (**b**)

and was not otherwise immunocompromised. The patient had lived her entire life in the Midwestern United States (US) and had no relevant travel history. She denied any significant occupational and recreational exposures, including to asbestos and recreational drugs. There was no prior history of malignancies, radiation or chemotherapy. She was up to date on her recommended cancer screening.

Her review of systems failed to demonstrate any evidence of fevers, chills, sweats, chest pain, weight changes or difficulties swallowing.

The patient's past medical history was significant for well-controlled hypertension, hyperlipidemia, osteoporosis, osteoarthritis and glaucoma. Her medications at presentation included: metoprolol 50 mg daily, furosemide 40 mg daily, gemfibrozil 600 mg twice a day, alendronate 70 mg weekly, calcium citrate 250 mg twice a day, acetaminophen 1,000 mg as needed, latanoprost eye drops daily and aspirin 81 mg daily.

General physical examination revealed a well-nourished woman in no acute distress. Her vital signs were height 156 cm, weight 69 kg, body mass index 28 kg/m^2, temperature 36.3°C, respiratory rate 15/min, heart rate 86/min, blood pressure 137/76 mmHg and oxygen saturation 89% on room air. Pulmonary examination demonstrated dullness to percussion and decreased breath sounds over the lower half of the right lung field and a few scattered crackles heard over the left lung base. Wheezes or rhonchi were absent. The remainder of the physical examination was normal.

Laboratory investigation showed a normal hemoglobin level, white blood cell count, platelet count, total protein, sodium, creatinine, calcium, alkaline phosphatase and aspartate aminotransferase level.

With the Presented Data, What Is Your Working Diagnosis?

Case 1 is an 80-year-old never smoker without any history of preexisting lung diseases, occupational and environmental exposures who presents with a spontaneous right-sided pneumothorax and associated pleural effusion – hydropneumothorax. Based on the absence or presence of any known lung disease spontaneous pneumothorax is classified as primary or secondary. Nevertheless it is important to recognize that the pneumothorax may be the initial manifestation of previously unrecognized lung diseases. The pleural effusion may simply be secondary to a persistent pneumothorax or part of the underlying lung disease. At this point the list of possible diagnoses remains long and includes airway diseases/emphysema, pulmonary infections (e.g., tuberculosis or pneumocystis jiroveci pneumonia), parenchymal lung diseases (e.g., sarcoidosis or idiopathic pulmonary fibrosis), connective tissue diseases (e.g., ankylosing spondylitis or Ehlers–Danlos syndrome) and malignancies (e.g., mesothelioma, sarcoma or bronchogenic carcinoma). Additional information from more detailed imaging by chest Computed tomography (CT) and pleural fluid analysis are needed to narrow the list of differential diagnoses.

Further Workup

CT of chest, abdomen and pelvis confirmed the presence of a moderate right-sided pleural effusion and pneumothorax. There was a 1.3 cm peripheral pulmonary nodule in the right apex medially. In addition there was volume loss in the right middle and lower lobes as well as pleural thickening/nodularity in the right middle lobe laterally. There was no mediastinal lymphadenopathy and the CT of the abdomen and pelvis were within normal limits (Fig. 6.2).

Ultrasound guided thoracocentesis removed 850 mL of serous fluid before the procedure had to be terminated due to chest pain. Pleural fluid analysis revealed an exudative pleural effusion: pleural fluid LDH 1,389 U/L, total protein 6.9 g/dL, and cholesterol 320 mg/dL. The pleural fluid cell count was 3,300 cells/μL [microl] (74% macrophages/monocytes and 18% other cells). Cytology of the pleural fluid showed clusters of atypical mesothelial cells on a background of acute inflammation. Immunostaining was positive for calretinin and negative for EpCAM (antibody clones MOC31 and Ber-EP4), CD15, thyroid transcription factor 1 (TTF-1) and Carcinoembryonic Antigen (CEA) [1]. The interpreting pathologist favored that the observed atypical mesothelial cells were reactive.

Thoracic surgery was consulted, and the patient underwent right thoracotomy. Inspection of the pleural cavity showed diffusely abnormal pleural surfaces. Diagnostic biopsies confirmed the presence of malignant cells (metastatic adenocarcinoma versus mesothelioma) and talc pleurodesis was performed. The final pathology demonstrated an epithelial type mesothelioma. Immunostaining was positive for calretinin, cytokeratin 5/6, Wilms tumor antigen-1 (WT-1) and negative for CD15, EpCAM (MOC13) and TTF-1 [1].

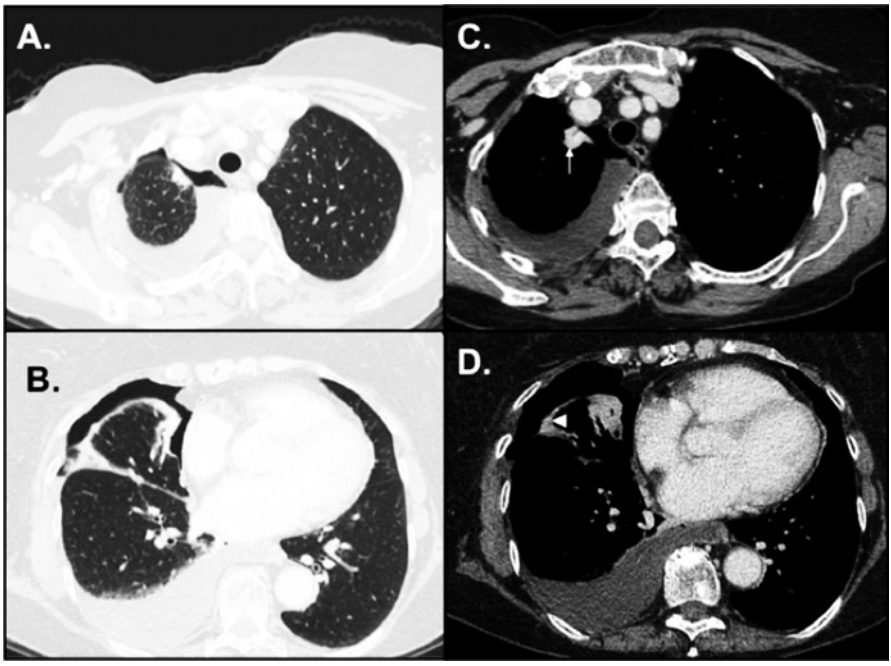

Fig. 6.2 Chest CT (lung – windows **a**, **b**; and mediastinal – windows **c**, **d**) confirmed the right-sided hydropneumothorax and demonstrated a 1.3 cm subpleural nodule in the right upper lobe (*white arrow*, **c**) and pleural thickening in the right middle lobe (*white arrow head*, **d**)

What Is Your Diagnosis and Why?

Chest CT imaging revealed pleural thickening and nodularity and pleural fluid analysis showed an exudative pleural effusion containing suspicious mesothelial cells. This raised the clinical suspicion for malignant pleural mesothelioma (MPM), which was ultimately confirmed based on the analysis of the histology and immunostaining of surgical pleural biopsy specimens.

Case continued: The patient's disease was clinically staged as T2, N0, M0 (Stage II) [2]. The patient's symptoms resolved following the surgical intervention. After a detailed discussion of the available therapeutic options, she elected observation and palliative therapy. Her management included repeated therapeutic thoracentesis for recurrent right-sided pleural effusions and pain management. The patient died 15 months after diagnosis.

Discussion

MPM is an uncommon, almost universally fatal malignancy originating from the mesothelial cells lining the pleural cavity. Approximately 3,300 cases of MPM are

diagnosed in the US annually [3]. In most cases MPM is associated with previous inhalational exposure to asbestos fibers 20–40 years preceding the diagnosis [3]. Asbestos typically occurs in the occupational environment either related to asbestos mining or milling or the exposure to manufactured asbestos products (e.g., plumbers, carpenters or military personnel). No history of or risk factors for asbestos exposure are identified in up to 30% of MPM patients. Other less common risk factors for MPM include prior thoracic radiotherapy for non-Hodgkin's lymphoma or germ cell tumors, oncogenic viruses (simian virus-40, SV-40) or genetic predisposition [3]. Whereas restriction of asbestos use by governmental regulation resulted in decreased exposure and a decline of MPM cases in the US the frequency of MPM continues to rise in other parts of the world. In the absence of effective screening programs most patients seek medical attention for complains of dyspnea and/or chest pain. Physical examination frequently reveals signs of a pleural effusion. The chest CT scan characteristically shows pleural thickening (100%) commonly >1 cm (53%) which involves the mediastinal pleura (95%) and interlobar fissures (72%). A pleural effusion is typically present as well (87%) [4]. Our patient presented with a right-sided hydropneumothorax, a uncommon initial manifestation of a primary or metastatic thoracic malignancy. In 1973 Dines and colleagues reported their review of 1,143 cases of spontaneous pneumothorax evaluated at the Mayo Clinic in Rochester over the preceding 20 years. Ten (0.9%) of these cases were attributable to pulmonary malignancies. Five patients had sarcomas, one had a lymphosarcoma and the remaining four patients had bronchogenic carcinomas. None of their patients had MPM. More recently, Hoag and colleagues identified 153 reported cases of spontaneous pneumothorax in patients with 20 different sarcoma cell types in the literature. The frequency of spontaneous pneumothorax in sarcoma patients varied between 1% and 3% [5]. Considering that bronchogenic carcinomas represent the most common malignancies in the US spontaneous pneumothorax is rarely seen in these individuals (<0.01%).

In MPM a number of case reports and small case series describe the occurrence of spontaneous pneumothorax. In a recent case series reporting the chest CT findings at initial presentation of 92 MPM patients the investigators detected a spontaneous pneumothorax in approximately 10% of patients suggesting that MPM is not uncommonly associated with this finding [4]. Even so the exact mechanism for the development of pneumothorax in MPM is unknown. It is likely attributable to direct pleural invasion and the development of a bronchopleural fistula. In contrast to other causes of spontaneous pneumothorax these cases are more likely to be refractory to standard therapy. Sheard and colleagues identified 5 unsuspected MPM cases among 91 consecutive pleurectomy specimens obtained during surgical procedures for recurrent pneumothorax [6].

Histologically MPM is typically classified into three subtypes: epithelioid, sarcomatoid and mixed. The epithelioid variant is most common (60% of cases). The histological confirmation of MPM can be rather challenging. Pleural fluid cytology and non-image guided pleural biopsy alone or in combination have only limited sensitivity, 26%, 21% and 39%, respectively [7]. Therefore a precise tissue diagnosis characteristically requires tissue sampling by surgical biopsy (video-assisted (VATS) or open) or image guided core needle biopsy. These procedures have a similar diagnostic yield [8].

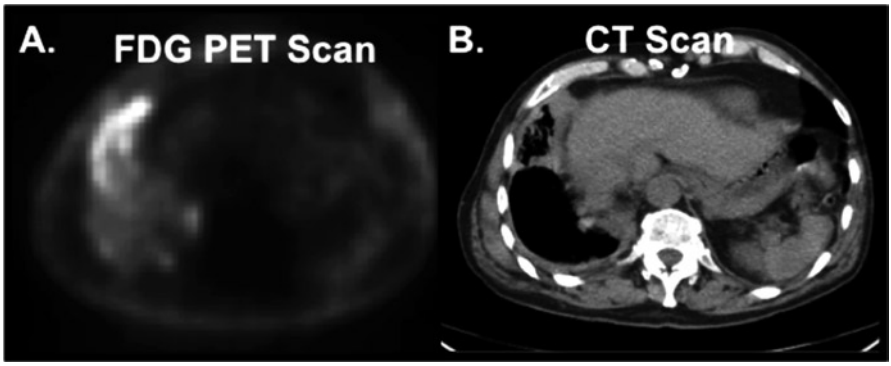

Fig. 6.3 CT/PET examination demonstrating nodular pleural thickening with increased metabolic activity (**a**, **b**)

The cytological and histological analysis of pleural fluid and pleural biopsy specimens remains challenging. Consequently immunostaining (is commonly utilized to increase the diagnostic yield. A typical immunostaining includes makers to confirm the mesothelial origin of the cells (e.g., calretinin, cytokeratin 5/6, WT-1 and podoplanin) in addition to makers to exclude alternative diagnosis (e.g., CD15 (adenocarcinoma), EpCAM (epithelial malignancies) and TTF-1 (non-small cell lung cancer)) [1].

Chest wall seeding at the biopsy site occurs in about 10% of patients and it remains unclear whether prophylactic local radiotherapy precludes this complication [8]. Increased metabolic activity by positron emission tomography (PET) scanning usually suggests the malignant character of a pleural abnormality [3] (Fig. 6.3).

Case 2

A 75-year-old man presented because of a 3-month history of progressive right-sided chest wall pain and shortness of breath. He had a history of a prior right-sided exudative pleural effusion, which had been extensively evaluated 3 years prior to presentation. The patient had negative pleural fluid analysis and VATS pleural biopsy followed by talc and mechanical pleurodesis. He was a lifetime non-smoker with a history of asbestos exposure for many years. As a young man he worked in the steam room of a ship in the Navy. Subsequently, he worked as a pipe fitter until his retirement in 1988. CT scan of the chest revealed right-sided nodular pleural thickening (Fig. 6.3).

These abnormalities were biopsied under CT guidance, but the results were non-diagnostic. A CT/PET examination showed increased metabolic activity of these nodules with a maximal standardized uptake value (SUV) of 4.9. In addition increased activity was observed in right hilar (N1), right lower paratracheal (N2) and subcarinal (N2) lymph nodes (Fig. 6.4).

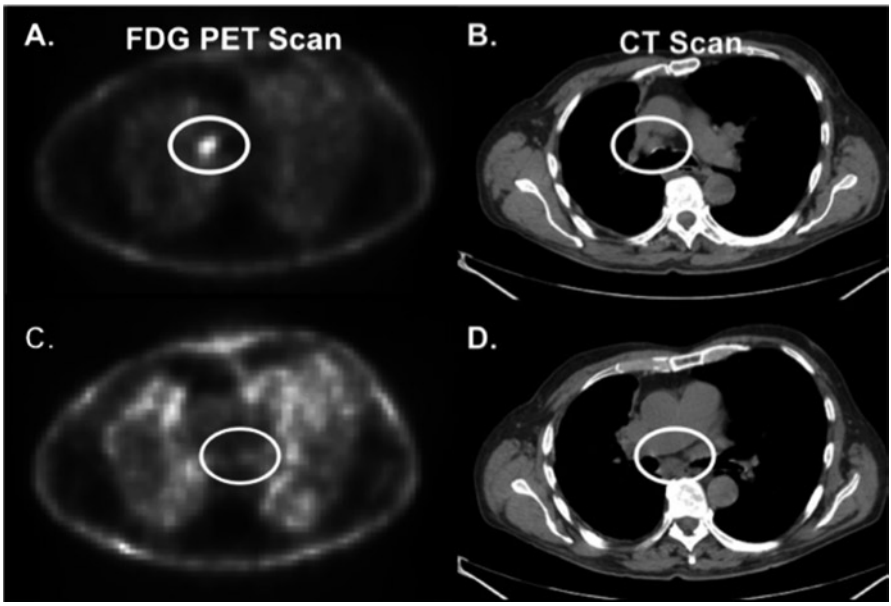

Fig. 6.4 CT/PET examination demonstrating increased metabolic activity (**a**, **c**, *white oval*) within radiographically enlarged (**b**, **d**, *white oval*) right lower pre-tracheal (mediastinal lymph node station 4R, N2, **a**, **b**) and subcarinal (mediastinal lymph node seven, N2, **c**, **d**) mediastinal lymph nodes

His past medical history was significant for prostate cancer treated with radical prostatectomy 12 years earlier, hypertension, asthma with aspirin allergy, lumbar spine surgery of degenerative disk disease and Dupuytren's contractures. There was no prior history of malignancies, radiation or chemotherapy.

At presentation the patient's medications only included: metoprolol 25 mg twice daily and hydrochlorothiazide 25 mg daily.

General physical examination revealed a well-nourished man in no acute distress. His vital signs were height 169 cm, weight 70 kg, body mass index 25 kg/m^2, temperature 35.9°C, respiratory rate 14/min, heart rate 68/min, blood pressure 173/87 mmHg and oxygen saturation 92% on room air. Pulmonary examination demonstrated diminished right-sided breath sounds and decreased right chest volume. The remainder of the physical examination was normal.

Laboratory investigation showed a hemoglobin level of 15 g/dL, white blood cell count 7×10^9/L, platelet count 379×10^9/L, calcium 10.4 mg/dL, sodium 133 mmol/L and a normal creatinine , alkaline phosphatase and aspartate aminotransferase level.

With the Presented Data, What Is Your Working Diagnosis?

Case 2 is a 75-year-old never smoker with significant occupational asbestos exposure and previous right-sided pleural disease/pleurodesis. He now presented with increasing

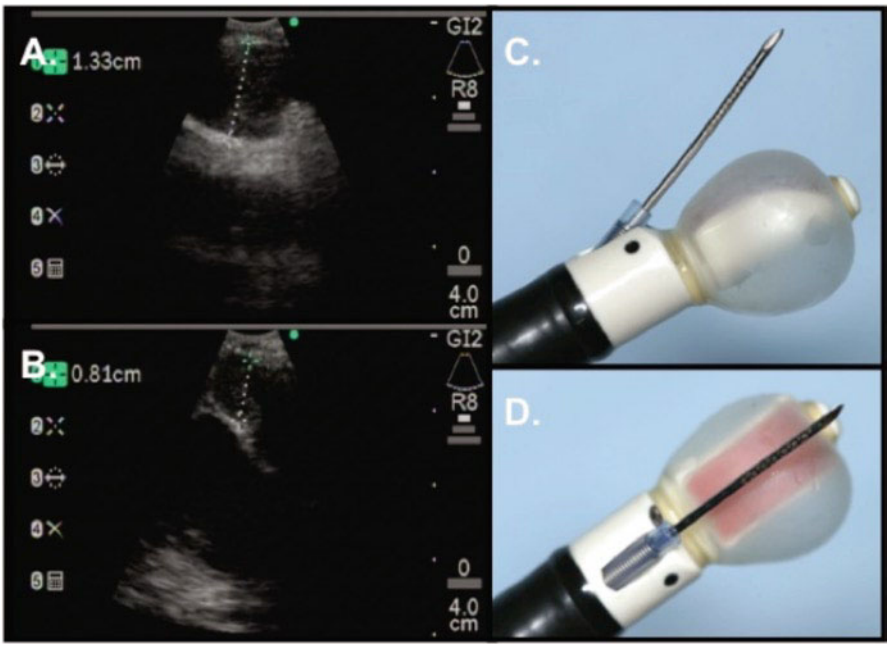

Fig. 6.5 Endobronchial ultrasound (EBUS) of subcarinal (**a**) and lower right pre-tracheal (**b**) mediastinal lymph nodes. EBUS bronchoscope with 22-gauge transbronchial biopsy needle (**c**, **d**)

right-sided chest pain and dyspnea. Chest imaging by PET-CT revealed a metabolically active pleural right thickening/nodularity with associated right hilar and mediastinal lymphadenopathy. Despite a non-diagnostic CT-guided core needle biopsy the clinical suspicion for MPM remains very high in this patient. Other considerations include metastatic disease to the right pleural space, benign asbestos-related pleural disease and chronic pleural space infection. A tissue diagnosis is needed. Given the previous pleurodesis and radiographically abnormal mediastinal lymph nodes bronchoscopy with endobronchial ultrasound (EBUS) was performed.

Further Workup

Flexible bronchoscopy did not demonstrate any endobronchial abnormalities. EBUS revealed a 1.3 cm subcarinal lymph node (mediastinal lymph node station 7, Fig. 6.5a) and a 0.8 cm lower right pre-tracheal mediastinal lymph node (mediastinal lymph node station 4R, Fig. 6.5b). Both lymph nodes were biopsied with 3 needle passes under ultrasound guidance (Fig. 6.5c, d).

Five milliliters of bloody fluid and 1.4 and 2.0 cm of tissue aggregates were obtained from the station 4R and seven lymph nodes respectively. Cytological examination established a diagnosis of epithelioid type MPM. Immunostaining was

positive for calretinin and podoplanin and negative for EpCam (MOC31& BerEP4), epithelial glycoprotein 2, EGP-2 (epithelial malignancies), TTF1 and CEA (adenocarcinomas) [1].

What Is Your Diagnosis and Why?

The clinically suspected diagnosis of MPM was confirmed by cytology and immunostaining of biopsy specimens obtained from enlarged and metabolically active mediastinal lymph nodes by EBUS guided TBNA. In addition to providing a diagnosis this procedure also confirmed N2 disease, which excluded the patient from any consideration of surgical resection.

Case continued: The patient's disease was staged as T1, N2, M0 (Stage III) and palliative chemotherapy with pemetrexed and cisplatin was recommended [2]. The patient opted to receive chemotherapy closer to home and was lost for follow up. He died 14 months after diagnosis.

Discussion

In our patient prior pleurodesis precluded VATS pleural biopsy and made open surgical biopsy more challenging. Moreover CT-guided core needle pleural biopsy was unfortunately non-diagnostic. Consequently, EBUS guided transbronchial needle aspiration (EBUS-TBNA) was employed to establish a diagnosis of MPM. Although, EBUS-TBNA of mediastinal and hilar lymph nodes has become an extremely valuable tool for the diagnosis and staging of lung cancer, its use for the diagnosis of MPM is restricted to a few case reports. A formal assessment of the diagnostic yield of EBUS-TBNA for MPM is lacking. This strategy may not only represent a non-surgical alternative for patients with suspected MPM with prior pleurodesis but also integrate the initial diagnosis and mediastinal staging of MPM.

MPM is currently staged using the Tumor (T), Lymph node (N) and Metastasis (M) staging system. TNM stage assists in predicting patient outcomes and in the identification of possible candidates to benefit from multimodality therapy (chemotherapy, surgical resection and radiation therapy) [2]. Imaging studies such as CT, PET, MRI and CT-PET are widely used for staging. Unfortunately the diagnostic performance of these techniques for T and N staging remains suboptimal and surgical staging using laparoscopy with peritoneal lavage followed by mediastinoscopy is recommended in some major centers prior to surgical resection of MPM. Yet even the diagnostic yield of mediastinoscopy only ranges between 30% and 80%. Recently, Rice and colleagues demonstrated that EBUS-TBNA might represent a valuable alternative for the mediastinal staging of MPM. With a sensitivity of 52% it outperformed mediastinoscopy, CT and PET in a series of 85 MPM patients [9]. Similarly, transesophageal endoscopic ultrasound guided fine needle aspiration

(EUS-FNA) of mediastinal lymph nodes was found to have a comparable diagnostic yield to surgical mediastinoscopy [10]. Therefore both EBUS-TBNA and EUS-FNA represent promising tools for the diagnosis and non-surgical mediastinal staging of MPM.

Unfortunately, the therapeutic outcomes of MPM remain limited. Despite the presence of distant metastasis at autopsy in 50% of MPM patients the morbidity and mortality of MPM is largely attributable to local disease progression. The median survival of patients with MPM ranges between 4 and 13 months. Currently available therapeutic interventions have only a small impact on natural disease progression.

Surgical approaches used include extrapleural pneumonectomy (EPP), which involves the en bloc resection of the ipsilateral lung, parietal pleura, pericardium and hemidiaphragm. It provides maximal cytoreduction and allows higher doses of postoperative radiotherapy. Nevertheless EPP is associated with significant peri- and postoperative morbidity and mortality (5–7%). In contrast, parietal pleurectomy and decortication provides less cytoreduction but can potentially improve compromised pulmonary function and is associated with less peri- and postoperative morbidity and mortality.

Whereas the benefit of an aggressive multimodality approach including neoadjuvant chemotherapy followed by surgical resection of macroscopic disease and adjuvant radiotherapy has been demonstrated in carefully selected MPM patients, the general role of this approach is controversial.

Recently two Phase III studies demonstrated moderate survival benefits of systemic chemotherapy in MPM patients. These studies demonstrated that combination chemotherapy using the folate antagonist pemetrexed or raltitrexed in combination with cisplatin may extend the survival of MPM patients by approximately 3 months and improves quality of life when compared to patients receiving cisplatin monotherapy [3]. Preliminary data suggest folate antagonists pemetrexed or ralitrexed that the benefit of chemotherapy is larger when treatment is initiated promptly following the diagnosis of MPM even in asymptomatic patients rather than being delayed until symptomatic disease progression.

Best supportive care of MPM mainly involves the symptomatic management of pain and dyspnea utilizing opiates and, if indicated, pleural fluid drainage/management by repeated therapeutic thoracocentesis, talc pleurodesis or placement of a permanent pleural catheter. In addition all MPM patients and their families benefit from psychosocial support.

Questions

1. Which of the following are possible causes of spontaneous pneumothorax?

   (a) Ruptured subpleural blebs
   (b) Primary or metastatic thoracic malignancies
   (c) Obstructive lung disease (asthma and COPD)
   (d) Certain pulmonary infections (Pneumocystis pneumonia or Tuberculosis)
   (e) All of the above

2. Which malignancies have been most frequently associated with refractory cases of spontaneous pneumothorax?

   (a) Lymphomas
   (b) Sarcomas
   (c) Bronchogenic carcinomas
   (d) Mesotheliomas
   (e) Breast Cancers

3. What is the approximate diagnostic yield of combined pleural fluid cytology and non-image guided pleural needle biopsy (Abrahams needle) for mesothelioma?

   (a) 5%
   (b) 20%
   (c) 40%
   (d) 60%
   (e) 80%

4. Which of the following statements regarding the pathogenesis of mesothelioma is *not* correct?

   (a) All patients with MPM have a history of asbestos exposure
   (b) MPM typically develops 20–40 years after asbestos exposure
   (c) SV40 virus may be involved in the pathogenesis of some MPM cases
   (d) Familial cases of MPM have been identified
   (e) Prior thoracic radiation therapy represents a risk factor for MPM

5. Which of the following statements applies to the diagnosis of MPM?

   (a) The diagnosis of MPM routinely requires an open surgical biopsy
   (b) Serum biomarkers such as osteopontin are valuable for MPM screening
   (c) Chest CT scan is helpful for MPM screening in high-risk individuals
   (d) The diagnostic yield of image-guided pleural biopsy is comparable to surgical biopsies
   (e) Prophylactic radiotherapy always prevents chest wall seeding after diagnostic biopsy

6. Which statement is true regarding the staging of MPM?

   (a) PET scan is an accurate tool for mediastinal staging
   (b) Pre-surgical laparoscopy and mediastinoscopy accurately identify all patients with peritoneal disease or mediastinal lymph node involvement
   (c) Endobronchial or transesophageal ultrasound guided biopsies of mediastinal lymph nodes are valuable tools for mediastinal staging
   (d) Chest CT scan accurately detects mediastinal lymph node involvement
   (e) All of the above

7. Which of the following are currently accepted first-line therapeutic approaches for selected patients with MPM?

   (a) Multimodality therapy (neoadjuvant chemotherapy, surgical resection and adjuvant radiotherapy)
   (b) Clinical trials and experimental therapy
   (c) Combination chemotherapy using a folate antagonist (e.g., pemetrexed and cisplatin)
   (d) Palliative therapy for symptom control only
   (e) All of the above

8. Which statement regarding the use of chemotherapy for MPM is *not* correct?

   (a) Single agent chemotherapy has never been shown to be superior to palliative care in MPM
   (b) Combination chemotherapy with pemetrexed supplemented with Vitamin B12/Folate and cisplatin is significantly more effective than cisplatin monotherapy
   (c) Combination chemotherapy extends patient survival by approximately 3 months
   (d) Combination chemotherapy improves quality of life
   (e) The start of chemotherapy should always be delayed until patient become symptomatic

9. Which statement regarding multi-modality therapy (adjuvant chemotherapy, surgical resection and adjuvant radiotherapy) is true?

   (a) Surgical options include extrapleural pneumonectomy or pleurectomy
   (b) The role and benefit of multi-modality therapy for MPM has been clearly established in randomized controlled trials
   (c) Therapy related morbidity and mortality of multi-modality therapy do not significantly impact therapeutic outcomes
   (d) If tolerated, current evidence favors extrapleural pneumonectomy over pleurectomy
   (e) All of the above

10. Which statement regarding the best supportive care for MPM patients is correct?

    (a) Pleural catheter placement can control dyspnea in MPM patients with recurrent symptomatic pleural effusions
    (b) Talc pleurodesis can relieve dyspnea
    (c) Pleurectomy and decortication can provide symptomatic improvement in MPM patients with restrictive lung function
    (d) MPM-related dyspnea can be treated with opiates
    (e) All of the above

Answer key: 1. (e), 2. (d), 3. (c), 4. (a), 5. (d), 6. (c), 7. (e), 8. (e), 9. (a), 10. (e)

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Part III
Infectious Diseases of the Lungs

Chapter 7
Pneumonia

Leah Chernin, David Swender, and Haig Tcheurekdjian

Abstract Pneumonia is an infection of the alveoli, distal airways and interstitium of the lung. The Infectious Disease Society of America/American Thoracic Society (IDS/ATS) consensus guidelines have established diagnostic and treatment recommendations for patients with community-acquired pneumonia. When treatment failures occur the physician must think outside these guidelines and reevaluate the patient for causes such as rare or atypical organisms, an impaired host immune response, or noninfectious causes of pneumonitis.

Keywords Pneumonia • Community-acquired pneumonia • Primary immunodeficiency • Pneumonia treatment failure • Dyspnea • *Streptococcus pneumoniae* • Viral pneumonia • Empyema

Case 1

The patient is a 38-year-old female with common variable immunodeficiency (CVID), Turner's syndrome, and asthma who presented with a 1-week history of progressive dyspnea and a nonproductive cough. The cough was diurnal without any nocturnal disruption. The patient denied wheezing and there was no improvement of the cough with albuterol treatment.

The patient's history was negative for smoking or secondhand tobacco smoke exposure. She had no history of environmental or occupational inhaled irritant

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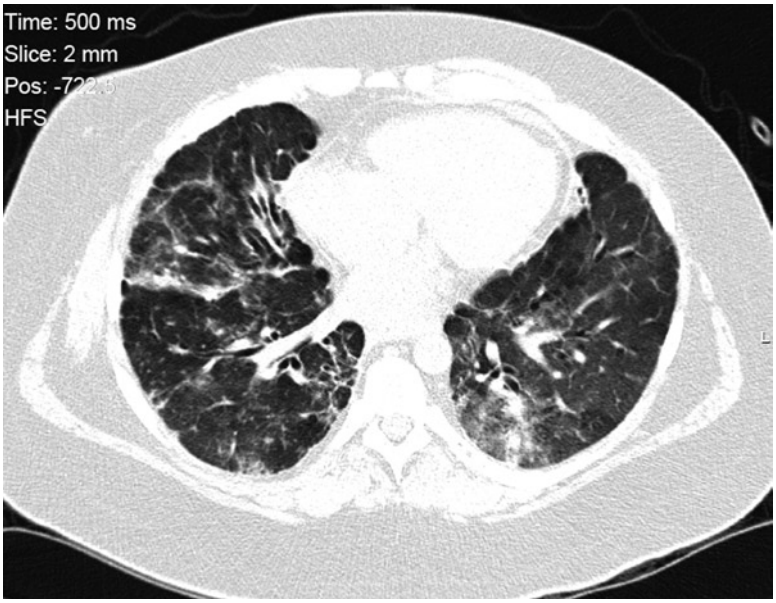

Fig. 7.1 Patchy infiltrates throughout the lung fields with ground glass opacities

exposures. There were no pets in the home environment and the patient denied any prolonged or recurrent exposure to animals.

Current medications included fluticasone propionate 500 mcg/salmeterol 50 mcg dry powder inhaler, one inhalation twice per day; tiotropium 18 mcg capsule, one capsule inhaled daily; montelukast 10 mg oral tablet daily; albuterol inhaled as needed; and intravenous immunoglobulin (IVIG) infusions monthly.

At presentation the patient was afebrile, with a heart rate of 92 beats/min, a respiratory rate of 20 breaths/min and an oxygen saturation of 98% on room air. On physical exam she appeared dyspneic; however, her cardiac as well as pulmonary exams were both unremarkable.

CT scan of the chest revealed a fine ground glass appearance throughout the lung fields as well as slightly enlarged mediastinal lymph nodes (Fig. 7.1). The patient was treated with an oral steroid taper and levofloxacin. The patient clinically improved with this treatment regimen but the cough did not completely resolve.

Approximately 1 month later the patient presented with a worsening cough and dyspnea. However, with this episode, the patient was found to be hypoxic with an oxygen saturation of 86% on room air. Her history was significant for at least a week of increasing dyspnea and a nonproductive cough. The cough again occurred primarily during the daytime hours with no nocturnal symptoms. The cough was not accompanied by any wheezing and there was no improvement with albuterol treatment. The patient also reported a temperature ranging from 100°F to 101°F.

At presentation the patient had a temperature of 101°F, a heart rate of 100 beats/min, a respiratory rate of 25 breaths/min, and she required 2 L of oxygen via

nasal cannula to maintain normal oxygen saturation. On physical exam the patient appeared dyspneic and in mild respiratory distress with occasional retractions. Her respiratory exam revealed inspiratory crackles throughout the lung fields. No wheezing was present. The remainder of her physical exam was unremarkable.

Initial laboratory evaluation included a complete blood count (CBC) with differential and electrolytes, all of which were unremarkable. Serum IgG level was therapeutic at a level of 850 mg/dL (normal range 650–1,400 mg/dL). A chest x-ray revealed a persistent prominence of interstitial markings which had increased from her previous radiologic exam.

With the Presented Data, What Is Your Working Diagnosis?

An immunocompromised host that presents with increasing dyspnea, a nonproductive cough, and chest x-ray findings of persistent and progressive prominent interstitial markings creates a broad and complex differential diagnosis for the clinician. The most prominent immune defect in CVID is the inadequate formation of immunoglobulins. This heightens the risk of infection by the most common infectious agents that cause pneumonia (i.e., encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae*). In addition to these organisms, infection in an individual with a primary immunodeficiency should also lead to the search for infectious agents and disease processes that might otherwise not be suspected in a patient with an intact immune response. Rare, atypical and opportunistic organisms must be considered as a cause for lung infiltrates such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella pneumophila*, *Pneumocystis jiroveci*, *Aspergillus*, or Cytomegalovirus.

Based on radiographic findings of prominent interstitial markings, the differential diagnosis of noninfectious processes should include sarcoidosis, idiopathic interstitial pneumonias, pulmonary fibrosis with connective tissue disease, pulmonary hemorrhage syndromes, lymphocytic infiltrate disorders, eosinophilic pneumonias, amyloidosis, drug-induced interstitial inflammation, hypersensitivity pneumonitis due to occupational or environmental exposures, and congestive heart failure.

Workup

The patient was admitted to the hospital for further evaluation and treatment. Upon admission to the hospital, viral polymerase chain reactions (PCR) for parainfluenza virus, influenza virus, respiratory syncytial virus, adenovirus and metapneumovirus were performed and were all found to be negative. Sputum and blood cultures were also negative.

Due to the patient's history of immunodeficiency, recent antibiotic treatment failure and progressive radiographic finding, bronchoscopy with bronchoalveolar lavage and biopsies was performed, but this was non-diagnostic. Subsequently, a video-assisted thoracoscopic surgery (VATS) with lung biopsy was performed.

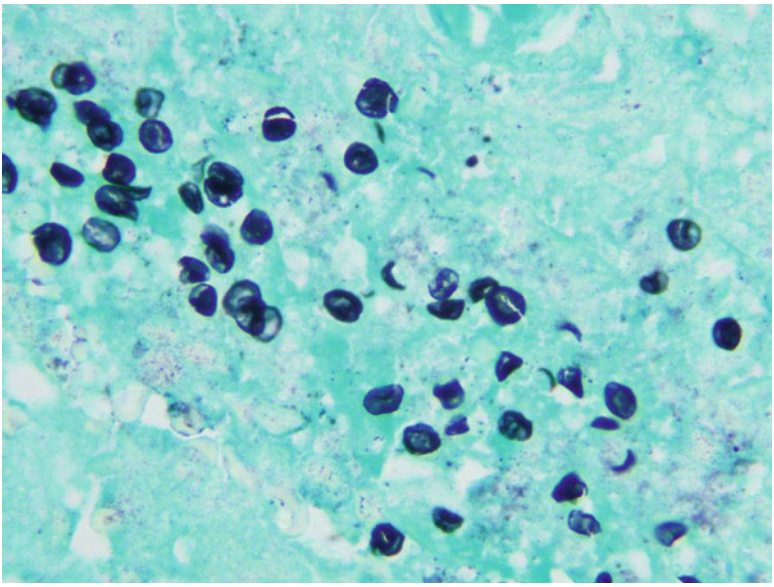

Fig. 7.2 100 × GMS stain demonstrates *Pneumocystis jiroveci* pneumonia

Gomorimethenamine silver stain revealed *Pneumocystis jiroveci* pneumonia (PJP) with abundant intraalveolar foamy macrophages and occasional neutrophils (Fig. 7.2). The biopsy also showed chronic interstitial pneumonitis with fibrosis, likely due to her history of CVID and recurrent infections. Fungal culture and acid-fast bacillus culture performed on the lung biopsy specimen were negative.

Once the diagnosis of PJP was established, peripheral T cell and B cell numbers were quantitatively evaluated by flow cytometry and testing for human immunodeficiency virus (HIV) by PCR was performed. The patient was found to have a normal number of T cells and B cells and was negative for HIV. It is important to note that HIV antibody testing may not be informative in an individual with an antibody deficiency because such individuals may not be able to produce antibodies against HIV, leading to false negative results. It is also important to recognize that patients with CVID may have functional T cell defects in spite of normal T cell numbers which can predispose them to an opportunistic infection, as demonstrated in this case.

What Is Your Diagnosis and Why?

Based on the lung biopsy results, the patient was diagnosed with PJP. The patient was successfully treated with trimethoprim-sulfamethoxazole 160 mg/800 mg two tablets by mouth three times per day for 21 days and with a prednisone taper. The prednisone taper started at 40 mg by mouth twice per day for 5 days, followed by

40 mg by mouth daily for 5 days, and then 20 mg by mouth daily for 11 days. Once the treatment of PJP was completed the patient was started on a prophylactic dose of one trimethoprim-sulfamethoxazole 160 mg/800 mg tablet daily.

Case 2

A 2-year-old male with a history of recurrent cutaneous staphylococcal abscesses and eczema presented to the emergency department with cough and fever. The patient first developed the cough 1 week prior, and it progressively worsened. There was no cyanosis or apnea, but the patient developed increased fussiness and fevers 1 day prior to arrival, with a temperature of 104°F.

On exam, the patient had a temperature of 103.8°F, a heart rate of 135 beats/min, a respiratory rate of 42 breaths/min, a blood pressure of 90/58, and an oxygen saturation of 93% on room air. The patient appeared alert but fussy. Auscultation of the heart demonstrated tachycardia with a normal S1/S2. Crackles were heard diffusely on the left, with decreased air exchange on the left. The child demonstrated tachypnea and intermittent nasal flaring. There was no digital clubbing.

Arterial blood gas analysis showed a pH of 7.35, pCO_2 of 32, paO_2 of 85. A CBC showed a white blood cell count (WBC) of 22,000 cells/μL (normal 6,000–17,500 cells/μL), hemoglobin (Hb) of 14 g/dL (normal 11.5–13.5 g/dL), and platelets of 250,000 (normal 150,000–400,000/L); band neutrophils were elevated on differential. Serum chemistries were within normal limits. A chest x-ray showed a left lower lobe pneumonia. The patient was admitted for intravenous ceftriaxone and discharged after 3 days to complete a 2-week course of oral amoxicillin/clavulanate.

Twenty-four hours after discharge, the patient returned to the Emergency Department due to persistent coughing and increased work of breathing. On exam, the patient was tired-appearing and pale. Pulmonary exam was significant for tachypnea, rales and rhonchi on the left, and moderate intercostal retractions. The patient was again admitted and treated with intravenous ceftriaxone and vancomycin.

CT scan of the chest demonstrated a left-sided empyema with loculation (Fig. 7.3). CBC showed an elevated WBC and serum immunoglobulin levels were normal except for an elevated IgE of 691 IU/mL (normal 0–29 IU/mL). Blood cultures were negative. The patient underwent a VATS procedure for decortication and chest tube drainage of the empyema. Fluid analysis demonstrated: pH 6.9 (normal 7.3–7.6), total cells 100, with 54% band neutrophils (normal <10%), lactate dehydrogenase (LDH) 1,500 U/L (normal <200 U/L), and glucose 22 mg/dL (normal 30–60 mg/dL). Fluid culture (bacterial, fungal, mycobacterial) results were negative, and no organisms were seen on microscopy. The chest tube was successfully removed, and the patient was discharged 3 days later on intravenous ceftriaxone and vancomycin.

One month after this discharge, the patient was readmitted for acute respiratory distress secondary to a tension pneumothorax from a bronchopulmonary fistula (Fig. 7.4). Six days after chest tube removal, a repeat CT scan of the chest demonstrated

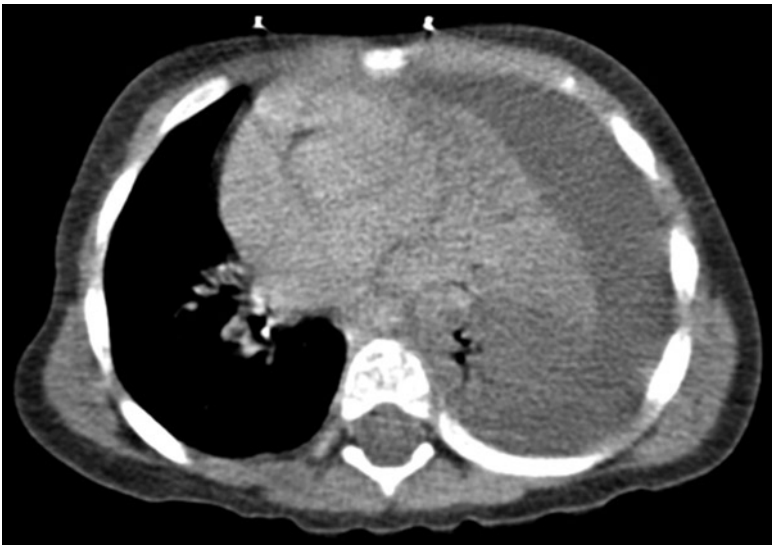

Fig. 7.3 CT of the chest, 24 h after initial discharge, showing a left-sided empyema with loculations

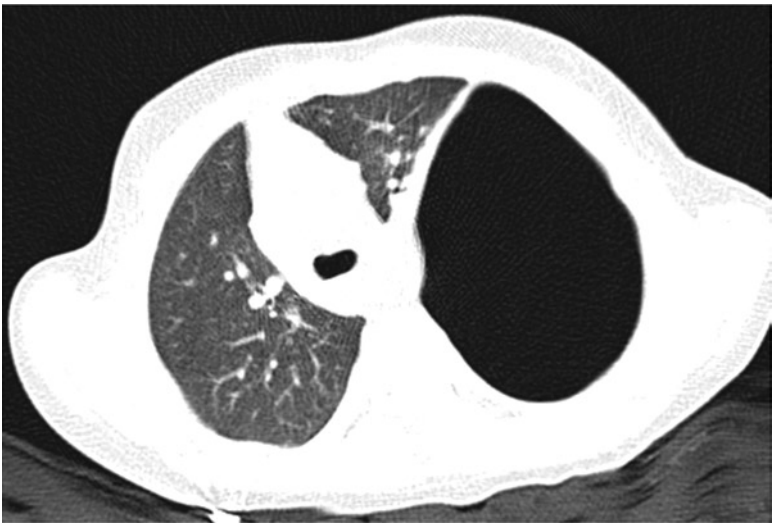

Fig. 7.4 CT of the chest, 1 month after discharge, demonstrating a tension pneumothorax secondary to a bronchopleural fistula

a hydropneumothorax on the left and new airspace disease on the right. The patient subsequently developed vomiting, fevers and lethargy, along with increased work of breathing. Pus was noted to be draining from the old chest tube site. A chest x-ray demonstrated recurrence of the empyema, and the patient underwent surgical drainage.

With the Presented Data, What Is Your Working Diagnosis?

The patient presents with recurrent pneumonia complicated by empyema without an identifying microbial pathogen. The diagnostic challenge is to determine whether host or pathogen factors are the primary cause of the recurrent infections.

Examples of host factors or illnesses that could result in or mimic recurrent pulmonary infections include: anatomic abnormalities (e.g., bronchogenic cyst, congenital lobar emphysema); recurrent aspiration; neuromuscular disorders; chronic pulmonary diseases (e.g., cystic fibrosis, pulmonary hemosiderosis, alveolar proteinosis); interstitial pneumonitis (e.g., bronchopulmonary dysplasia, hypersensitivity pneumonitis); immunodeficiency, or heart failure.

Pathogen factors can also result in failure of empiric antibiotic therapy. One must consider inadequate antibiotic coverage for resistant or uncommon bacterial pathogens. Uncommon pathogens such as *Legionella species* and *Pneumocystis jiroveci* require both specific testing and tailored antimicrobial therapy. Viral pneumonias should also be considered in the case of antibiotic failure.

The patient's presentation is highly suspicious for a primary immunodeficiency. With the history of eczema at birth, multiple staphylococcal abscesses, elevated serum IgE level, and now pulmonary infections with empyema, Hyper-IgE Syndrome (HIES) is high on the differential. Wiskott–Aldrich syndrome, another primary immunodeficiency, can also present in a similar manner; however, these patients invariably have thrombocytopenia with small platelets.

Workup

Culture of the fluid collected from the surgical drainage of the empyema demonstrated mixed anaerobes including *Bacteroides*. The patient was successfully treated with a prolonged course of intravenous piperacillin/tazobactam and vancomycin.

Allergy/Immunology was consulted. A genetic analysis detected a mutation in the signal transducer and activator of translation-3 (STAT3) gene. The patient was placed on IVIG and prophylactic antibiotics which led to a long-term decrease in the number and severity of skin and pulmonary infections.

What Is Your Diagnosis and Why?

This patient suffered from recurrent pneumonias and empyemas secondary to an inadequately treated initial pneumonia in the setting of an underlying primary immunodeficiency. On presentation, the patient received appropriate antimicrobial coverage for a pneumonia in an immunocompetent individual, but consideration should have been given to broader antimicrobial coverage considering the patient's history of recurrent infections with staphylococci.

The patient's clinical findings in conjunction with a STAT3 gene mutation confirm the diagnosis of HIES. This most commonly is caused by a sporadic or autosomal dominant mutation in STAT3, an important signal transducer in leukocytes, resulting in impaired cytokine signaling. HIES is characterized by severe, eczematous rash early in life, recurrent skin abscesses that are frequently "cold" (absent neutrophils), recurrent sinopulmonary infections, and typical facial features (broad nasal bridge, coarse facies, prominent forehead). Bacterial infections are frequently caused by staphylococci and primarily affect the skin and lungs. Interestingly, the presence of a bronchopleural fistula leading to a pneumothorax in this patient is concerning for a ruptured pneumatocele, the development of which is common in HIES.

Although initial pleural fluid cultures were negative, it is most likely that the initial pneumonia was caused by *Staphylococcus aureus*. Because of initially inadequate anti-Staphylococcal antibiotic coverage and the underlying immunodeficiency, this patient suffered from recurrence of the empyema, multiorganism involvement, and difficulty in clearing the infection.

Discussion

Pneumonia is defined as an infection of the alveoli, distal airways and interstitium of the lung. Clinical manifestations include cough, pleuritic chest pain, sputum production, and exam findings such as fever, auscultatory crackles, wheezes, and tachypnea. Visualization of infiltrates on radiography is required to confirm the diagnosis. Pneumonia is typically categorized as either community-acquired pneumonia (CAP) or nosocomial/healthcare-associated pneumonia [1]. These categories assist in anticipating potential etiologies of the pneumonia. CAP alone represents a significant health care burden, affecting 4 million adults/year in the United States, costing up to $10 billion.

Several factors are important in diagnosis and determination of etiology in a patient where pneumonia is suspected. These include both pathogen and host characteristics. As mentioned previously, the setting in which the pneumonia is contracted plays a role in determining suspected pathogens. In community-acquired pneumonia, common pathogens include: *Streptococcus pneumoniae, Haemophilus influenzae*, *Staphylococcus aureus*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Moraxella catarrhalis*, *Legionella spp.*, and aerobic gram-negative bacteria. Viral agents include *influenza*, adenovirus, parainfluenza and respiratory syncytial virus [1]. *Streptococcus pneumoniae* accounts for about 50% of cases admitted for CAP [2]. Overall, an infectious etiology is not determined in 70% of CAP cases.

Host factors are also an important consideration in evaluating pneumonia. The human lungs cover a surface area of 70 m^2 exposed to the environment. Host defenses in the lung include innate and acquired mechanisms. Innate defenses include anatomic barriers (nasal turbinates, mucociliary transport system, glottis) as well as cellular defenses (e.g., neutrophils, dendritic cells, macrophages). Surfactant plays an important role in the opsonization of bacteria. Alveolar macrophages monitor and

attack foreign substances, and also play a role in acquired immunity, presenting antigens to T cells for production of specific, long-lasting immune responses.

The adaptive immune system is centered upon producing a robust, antigen-specific response to foreign pathogens. Antigen presenting cells Phagocytose pathogens and present peptides from these pathogens to T cells. Activated T cells then interact with B cells to induce them to become immunoglobulin-secreting plasma cells or memory B cells. Immunoglobulins can then help to opsonize bacteria, assisting in destruction of the invading organism. Long-lived memory B cells migrate to the bone marrow, where they can quickly give rise to specific immunoglobulin-secreting plasma cells during future infections.

The Infectious Disease Society of America and American Thoracic Society (IDS/ATS) Consensus Statement provides guidelines in the management of community-acquired pneumonia [1]. This includes recommendations on diagnosis, empiric therapy, and management of nonresponding or severe pneumonia.

Diagnosis

The presentation of pneumonia can vary from mild respiratory illness to respiratory failure. Typically, CAP presents with cough, fever, sputum production, and pleuritic chest pain. It is important to note, however, that elderly and immunodeficient patients may not present with classic symptoms and signs.

A chest x-ray is typically needed to confirm the diagnosis of pneumonia. When a chest x-ray is negative in the presence of strong clinical suspicion, CT scan of the chest may be more sensitive in detecting pathology. When a patient is admitted to the hospital with a clinical presentation of pneumonia and the chest x-ray is found to be negative, empiric antibiotic treatment for pneumonia could be initiated with a repeat chest x-ray performed within 24–48 h.

Pulse oximetry should also be obtained to screen for hypoxic patients. The patient's oxygen saturation on room air is a vital piece of information when trying to establish whether a patient requires a hospital admission in addition to what level of in-patient care is warranted. Those patients who show signs of severe respiratory distress and require extensive respiratory support should be admitted to the intensive care unit.

Another facet of the diagnosis of pneumonia involves determining the etiology of the infection. The joint guidelines recommend screening cultures (blood, sputum) only when a specific pathogen is strongly suspected, or in circumstances where obtaining a specific pathogen will significantly alter the management of the patient. While empiric antibiotic coverage is often adequate, various clinical situations warrant further diagnostic evaluation to establish etiology. Some of these include: ICU admission, failure of outpatient antibiotic therapy, cavitary infiltrates on imaging, leukopenia, pleural effusion, or asplenia. Immunodeficient patients also warrant a more aggressive diagnostic approach. For example, patients with suspected or known T cell deficiency should be tested for fungal (e.g., *Pneumocystis jirovecii*) or viral etiologies (e.g., cytomegalovirus).

Table 7.1 IDS/ATS treatment recommendations

I.	Outpatient treatment
	1. Previously healthy, no comorbid conditions, no recent antibiotic use (past 3 months)
	Macrolide
	Doxycycline
	2. Comorbid conditions or recent antibiotic use (previous 3 months)
	Fluoroquinolone
	β-lactam plus macrolide
II.	Non-ICU inpatient treatment
	Fluoroquinolone
	β-lactam plus macrolide
III.	ICU inpatient treatment
	β-lactam plus azithromycin
	β-lactam plus fluoroquinolone
IV.	*Pseudomonas* is suspected
	Antipseudomonal, antipneumococcal β-lactam plus fluoroquinolone
	Antipseudomonal, antipneumococcal β-lactam plus aminoglycoside and azithromycin
	Antipseudomonal, antipneumococcal β-lactam plus aminoglycoside and antipneumococcal fluoroquinolone

Treatment

The initial treatment of pneumonia depends on the clinical setting, severity of illness, and host factors. These recommendations for empiric therapy are summarized in Table 7.1. Other factors that may influence antibiotic choice could include history of aspiration (gram-negative enteric bacteria), animal and travel exposures, and local microbial resistance trends. As illustrated in the above cases, patients with compromised immune systems warrant a more aggressive treatment strategy. Consideration should be given to empiric coverage with anti-fungal and anti-viral therapies, especially while cultures and antigen testing are pending. Coverage for pathogens depends upon the suspected (or known) immunodeficiency, and prophylaxis with intravenous immunoglobulin and/or antimicrobials is an important part of infection prevention for these patients.

Treatment Failure

Failure to respond to the initial antibiotic regimen for CAP has been shown to occur in 6–15% of hospitalized patients. A nonresponding pneumonia or treatment failure describes a lack of clinical improvement in the face of adequate antibiotic treatment. Two patterns of nonresponding pneumonias may occur. The first category encompasses those patients who clinically deteriorate or in whom the disease state progresses; the second describes those who fail to improve. Treatment failure is further classified as early failure, occurring in the first 72 h of treatment, or delayed failure, occurring greater than 72 h after starting treatment [1].

When a treatment failure occurs, diagnostic considerations should be expanded. One has to consider: resistant organisms, nosocomial superinfection, inappropriate antibiotic coverage, exacerbations of comorbid conditions, misdiagnosis, and inadequate host response. Conditions such as chronic obstructive pulmonary disease, asthma, pulmonary embolism, congestive heart failure, and endocarditis should also be considered in the differential diagnosis based on the patient's clinical presentation.

If the IDS/ATS treatment guidelines are followed, an abnormal host response is the most common cause of antibiotic failure [1]. An immunodeficiency should be suspected in those patients with a history of recurrent infections. Patients with a history of two or more pneumonias per year or patients who require intravenous antibiotics to eradicate infections should clue the physician in on the need for an immune evaluation [2]. Additional warning signs pointing toward a diagnosis of an immunodeficiency include an antibiotic failure to common organisms, infections with rare organisms, or an infection that progresses out of the realm of what is expected for that particular organism. Complications including pleurisy, bronchospasm, bronchiectasis, empyema, and pneumatoceles have been seen in patients with common variable immunodeficiency (CVID) as well as with other immunodeficiencies [3].

Primary immunodeficiencies currently affect 1 in 500 people [2]. Among primary humoral immunodeficiencies, a history of sinopulmonary infection is present in 62–84% of patients prior to diagnosis [3, 4]. Therefore, patients with recurrent sinopulmonary infections require an evaluation for a primary immunodeficiency. The most commonly encountered primary immunodeficiencies include selective IgA deficiency and common variable immunodeficiency.

Selective IgA deficiency is defined as a decreased or absent serum IgA level with normal IgG and IgM. Clinical manifestations of selective IgA deficiency can range from asymptomatic to severe recurrent sinopulmonary infections. Common variable immunodeficiency is characterized by recurrent sinopulmonary infections, hypogammaglobulinemia of at least two isotypes (IgG, IgA, or IgM), and impaired antibody function [5]. Patients with CVID frequently present with recurrent sinopulmonary infections in either mid-childhood or early adulthood. Primary immunodeficiencies can be inherited, so a detailed family history should be conducted on these patients. The evaluation of a patient with a suspected immunodeficiency should be conducted in consultation with an allergist/immunologist experienced in treating such disorders.

More invasive diagnostic considerations should also be considered when a treatment failure occurs. Bronchoscopy with bronchial alveolar lavage is a diagnostic option that could be used to attempt to identify a causative organism. Based on the clinical presentation and diagnostic findings, a VATS procedure with lung biopsy is another option that could also be performed to establish a diagnosis.

Pneumonia is a commonly encountered and often easily treated medical condition. The IDS/ATS guidelines provide the physician with an excellent framework to establish a diagnosis and treatment plan for most patients with pneumonia. However, when treatment failures occur one must think outside of the commonly encountered pathogens and look further for rare organisms, alternative diagnoses, and must remember to always evaluate the host's immune response.

Questions

1. Which of the following is an indication to identify the causative organism for a pneumonia?

   (a) Fever greater than 102°F
   (b) Admission to the hospital
   (c) Failure of empiric antibiotic coverage
   (d) Purulent sputum production
   (e) Pulse oximetry of 88% on room air

2. Which of the following pulmonary pathogens are classically associated with Hyper-IgE Syndrome?

   (a) *Bacteroides*
   (b) *Legionella* species
   (c) *Staphylococcus aureus*
   (d) *Cytomegalovirus*
   (e) *Mycoplasma pneumoniae*

3. Which of the following medications would be appropriate empiric antibiotic therapy for a patient who recently failed treatment of pneumonia with doxycycline and is clinically stable for outpatient therapy?

   (a) Amoxicillin/clavulanate plus azithromycin
   (b) Cefdinir plus levofloxacin
   (c) Ampicillin/sulbactam
   (d) Ceftriaxone
   (e) Doxycycline plus azithromycin

4. Which of these patients is NOT at increased risk for *Pneumocystis jiroveci* pneumonia?

   (a) A 58-year-old female on 20 mg prednisone daily for rheumatoid arthritis
   (b) A 9-year-old male undergoing induction chemotherapy for bone marrow transplant
   (c) A 73-year-old male receiving rituximab for rheumatoid arthritis
   (d) A 14-year-old male with selective IgA deficiency
   (e) A 66-year-old female with a history of diabetes mellitus type II and HIV infection

5. Which test result is indicative of *Legionella* pneumonia?

   (a) Induced sputum showing marked eosinophilia
   (b) Positive urinary antigen testing
   (c) Biopsy of lung tissue showing gram-positive cocci
   (d) Bronchoalveolar lavage (BAL) fluid showing hemosiderin laden macrophages
   (e) Thoracentesis with fluid analysis showing a cell count of 200 cell/HPF

6. Which of the following is not considered a common cause of CAP?

   (a) *Streptococcus pneumonia*
   (b) *Haemophilus influenzae*
   (c) *Staphylococcus aureus*
   (d) *Pneumocystis jiroveci*
   (e) *Mycoplasma pneumonia*

7. Which of the following is considered an innate anatomical barrier?

   (a) Nasal turbinates
   (b) T cells
   (c) B cells
   (d) Natural killer cells
   (e) Macrophages

8. If a patient clinically presents with pneumonia, but the chest x-ray is found to be negative and empiric antibiotics are initiated, when should a repeat chest x-ray be performed?

   (a) 12–24 h
   (b) 24–48 h
   (c) 48–72 h
   (d) 1 week

9. *Pneumocystis jiroveci* pneumonia is an opportunistic organism that is associated with a defect in what part of the immune system?

   (a) B cells
   (b) Natural killer cells
   (c) Macrophages
   (d) T cells
   (e) Neutrophils

10. Common variable immunodeficiency is associated with all of the following EXCEPT?

    (a) Eczema
    (b) Hypogammaglobulinemia
    (c) Recurrent pneumonia
    (d) Recurrent sinusitis
    (e) Opportunistic infections

Answer key: 1. (c), 2. (c), 3. (a), 4. (d), 5. (b), 6. (d), 7. (a), 8. (b), 9. (d), 10. (a)

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Chapter 8
Tuberculosis in Immunocompromised Hosts

Stratos Christianakis, Josh Banerjee, James S. Kim, and Brenda E. Jones

Abstract The diagnosis and treatment of tuberculosis in immunocompromised patients is often challenging. Although HIV infection is the greatest risk factor for TB; there are a growing number of cases of TB in patients on immunosuppressive therapy. Here we present two challenging cases of tuberculosis in immunocompromised hosts.

Keywords HIV/AIDS • Tuberculosis • Immune reconstitution inflammatory syndrome • Antiretroviral therapy

Case 1

Our patient is a 34-year-old Latino male who was admitted in February 2009 with a cough and fever for 2 months. The cough was intermittent and productive of white phlegm. His symptoms included a "lump" under his left arm which was painful. He also reported a weight loss of 30 lbs over 2 months.

His past medical history was significant for nose surgery 2 years prior to admission. Family history: His father had diabetes. His brother had tuberculosis in 2008. His cousin had leukemia.

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Social and Environmental History

The patient was born in El Salvador and completed 3 years of medical school. He immigrated to the United States 11 years ago. He worked at McDonald's in Los Angeles, but had been unemployed for most recently for 2 years. The patient is divorced and has one child. He lives with his brother. He stopped drinking alcohol 9 months ago, after previously drinking six to seven beers per week for 2 years. He does not use tobacco or other recreational drugs. His relevant sexual history is heterosexual.

Review of Systems

He also reported a rash on his face for 6 weeks, spreading to his arms and then legs. The rash was initially "itchy," but on admission he had no symptoms of pruritus. The rash previously on his torso had resolved without any topical treatment.

Physical Examination

He was a well-developed cachectic male with a slightly depressed affect. Vitals: Temperature: 103.4 F, pulse: 110, RR: 24, BP: 124/60. HEENT: The HEENT exam was normal. Lymph nodes: There was a 7 × 8 cm left axillary mass which was mildly tender and fluctuant. There were shotty right cervical lymph nodes. Heart had a regular rate and rhythm with a grade III/VI murmur at the left lower sternal border. Auscultation of the chest revealed normal breath sounds with occasional coughing during deep inspiration. Abdomen: Mild distension with decreased bowel sounds. The abdomen was soft with left upper quadrant tenderness and possible splenomegaly. Skin: Diffuse hyperpigmented excoriated lesions on face, arms, torso, legs, palms, and soles of feet. The lesions were macules and papules. The remainder of the examination was within normal limits.

Diagnositic Testing

Laboratory Data

Chemistry: Glu 121 (65–99) mg/dL, Alk Phos 270 (30–100) U/L, Total Protein 9.1 (6.0–8.0) g/dL, Alb 3.0 (3.5–5.0) g/dL, AST 37 (10–40) U/L, ALT 75 (5–40) U/L

Hematology: WBC 4.2 (3.7–10.3) K/mm^3, Hgb 9.0 (11.8–14.7) g/dL, HCT 26.9 (36.0–44.0) %, Platelets 257 (150–350) K/mm^3

Serologic studies: Positive RPR 1:64 (nonreactive), FTA-ABS reactive

Positive HIV: Elisa confirmed with Western Blot
HIV viral load 1,489,300
CD4 cells 84 (619–1,500)/mm^3

Chest radiograph: Small ill-defined infiltrate in the left lower lobe
Tuberculin skin test (PPD): negative (0 mm)

Impression

This is a newly diagnosed HIV-positive patient who presented with a left axillary mass. He also had a cough and fever. Although the chest radiograph was read as negative, the patient was placed in isolation and two induced sputums were obtained for acid fast bacilli (AFB) smear and culture. Both sputum smears were negative for AFB.

On admission, the patient was diagnosed with syphilis (RPR 1:64, FTA-ABS reactive) which was consistent with the macular and pustular rash of secondary syphilis. A lumbar puncture was obtained to also evaluate for neurosyphilis. The cerebral spinal fluid had an unremarkable cell count, glucose, protein, and the VDRL was negative. The patient received 2.4 MU of benzathine penicillin for the treatment of secondary syphilis.

Plan

On the fifth day of admission, the patient was sent to Pathology for a fine needle aspirate of the left axillary mass. The AFB smear was positive. The patient was started on tuberculosis medications: isoniazid, rifampin, ethambutol, and pyrazinamide, with pyridoxine (vitamin B6). Three additional sputum samples were sent on three separate days to clear the patient from isolation according to hospital policy. All of the sputum samples were negative for AFB. The patient was discharged from the hospital on tuberculosis medications and referred to Public Health Clinic. He was started on oral Bactrim DS once daily for prophylaxis against *Pneumocystis* pneumonia and toxoplasmosis. He was also referred to the HIV clinic for follow-up and to start antiretroviral therapy (ART).

The diagnosis of tuberculosis was made with a fine needle aspirate of the left axillary lymph node (positive AFB smear) which subsequently grew out *Mycobacterium tuberculosis* (MTB). One of the five sputum samples (negative AFB smears) also grew MTB. The Public Health Clinic was to continue directly observed therapy (DOT) with isoniazid 300 mg, rifampin 600 mg, pyrazinamide 1,500 mg, and ethambutol 1,200 mg, with pyridoxine (vitamin B6) 50 mg daily for the 2-month induction phase of therapy, followed by isoniazid and rifampin (for a drug susceptible isolate) for 4 months in the continuation phase to complete a 6-month course

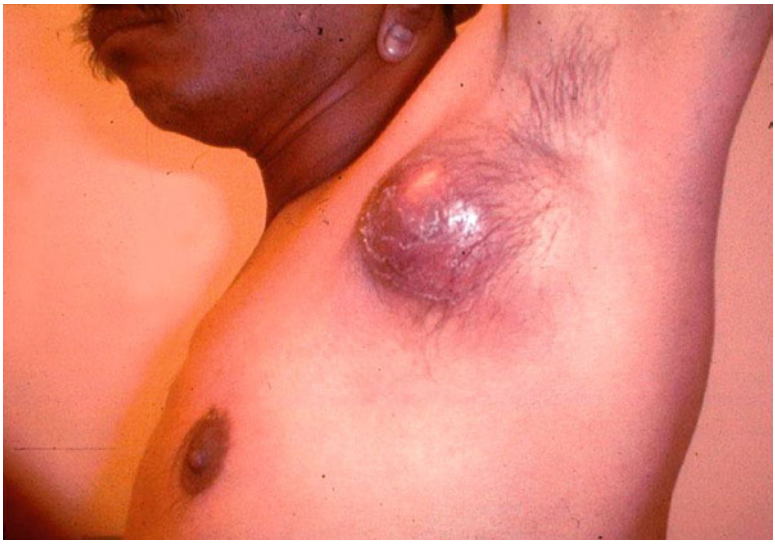

Fig. 8.1 Left axillary mass

of therapy. After 4 weeks, he was tolerating his TB regimen well and had noted a 10 lb weight gain. His fever, cough, and night sweats had resolved. On physical exam, his left axillary mass had improved dramatically. The size of the mass had decreased from 7 × 8 cm to 3 × 4 cm.

Antiretroviral therapy (ART) was prescribed 4 weeks after the initiation of antituberculous treatment. The patient was started on Atripla, a combination of three HIV medications: Sustiva (efavirenz), Emtriva (emtricitabine), and Viread (tenofovir).

Three weeks after beginning ART, the patient presented with fever, night sweats, weight loss, and an enlarging and painful left axillary lymph node.

Physical examination

Vital signs: 98.8 F, P 110, RR 18, BP 95/60, Wt 134 lbs
Lungs: Clear
Lymph nodes: 8 × 9 cm left axillary mass. The mass was erythematous, fluctuant, and painful on palpation (Fig. 8.1). Multiple small right cervical lymph nodes were also noted

Data

Laboratory Data

WBC 4.2 (3.7–10.3) K/mm^3, Hgb 9.0 (11.8–14.7) gm/dL, HCT 26.9 (36.0–44.0)%, Platelets 257 (150–350) K/mm^3

CD4 cells 120 (619–1,500)/mm^3
HIV RNA 840
Chest radiograph showed a new right pleural effusion

With the Presented Data, What Is Your Working Diagnosis?

Our patient initially improved on TB medications; however, the mass increased in size approximately 3 weeks after HIV medications were started. He also developed a new right pleural effusion. He also had modest fever and night sweats. He had an excellent response to ART with a significant decrease in the HIV viral load.

Differential Diagnosis

The differential diagnosis includes the emergence of drug-resistant tuberculosis, nontuberculous mycobacteria, lymphoma, Kaposi's sarcoma, superimposed bacterial infection/abscess with Methicillin-resistant *Staphylococcus aureus* (MRSA), cat scratch disease, fungal diseases (cryptococcosis and coccidioidomycosis).

Workup

A repeat fine needle aspiration of the left axillary mass was again positive for AFB but did not grow MTB.

What Is Your Diagnosis and Why?

Drug-Resistant Tuberculosis

The patient had worsening of symptoms while on isoniazid, rifampin, pyrazinamide, and ethambutol. Drug-resistant tuberculosis could be possible, although it seems less likely because of the initial improvement of symptoms. The patient was also on DOT with the public health department. All medication doses were observed as taken by the community worker assigned to the patient. It might be of concern that starting ART could have affected drug levels of the TB medications, but this is less likely given the efavirenz-based regimen which works well with rifampin. Other regimens which depend on the administration of protease inhibitors (PIs) combined with reduced doses of rifabutin are more likely to lead to drug resistance. The susceptibility results of the initial MTB isolate were not yet available.

Nontuberculous Mycobacteria (NTM)

The most common NTM would be *Mycobacterium avium* complex (MAC) which frequently causes lymphadenopathy. However, the medications rifampin and ethambutol would have some activity against MAC. Also the initial isolate from the left axillary lymph node grew *M. tuberculosis*. Although possible, it would be unlikely to have the emergence of a new NTM.

Malignancy

Kaposi's sarcoma and lymphoma were not seen on the fine needle aspiration.

Bacterial Infections

MRSA and cat scratch disease (*Bartonella henselae*) were not found on the lymph node aspirate.

Fungal Infections

Cryptococcus and coccidioidomycosis were also not isolated.

The MTB susceptibilities were obtained for the initial MTB isolate from the left axillary lymph node after 8 weeks, indicating the organism was susceptible to the TB medications. MTB also grew from the two induced sputums, although both were negative for AFB.

The diagnosis of immune reconstitution inflammatory syndrome (IRIS) was made after reevaluation and exclusion of the TB treatment failure and other opportunistic infections as the cause of his recurrent symptoms. The patient was scheduled for incision and drainage of the left axillary mass; however, there was spontaneous draining several days later. The patient's symptoms of fever and night sweats also resolved. He continued to have several "flares" of the left axillary mass which would swell intermittently during the TB treatment. The mass continued to drain spontaneously. The patient completed 6 months of TB treatment and continued to do well on ART.

Discussion

IRIS is also known as a paradoxical reaction which was reported in tuberculosis patients even before HIV/AIDS. A paradoxical reaction is defined as the worsening of the symptoms and lesions of tuberculosis while on treatment for TB. The cause is felt to be the recovery of the delayed hypersensitivity response and an increase in exposure and reaction to mycobacterial antigens after bactericidal TB therapy is initiated.

A similar response is described in patients with HIV-related TB. IRIS tends to occur a few weeks after the initiation of ART in patients coinfected with HIV and TB. Patients who are at highest risk for IRIS often have low CD4 counts and a high viral load when ART is initiated. The early initiation of ART after the diagnosis of TB is also a risk factor for IRIS. The most common manifestations are fever, lymphadenopathy, and new infiltrates on chest radiographs. IRIS is also associated with restoration of tuberculin reactivity. The AFB smears of new lesions are often positive, but the MTB culture negative as with our patient, which suggests an immune response to the MTB antigen.

IRIS also occurs in HIV patients with other opportunistic infections such as MAC, cytomegalovirus (CMV) retinitis, and cryptococcal meningitis. The treatment for IRIS depends upon severity of the symptoms; may include observation, nonsteroidal medications, or steroids. IRIS occurs in approximately 10–30% of patients with HIV-related tuberculosis [1, 2].

Considerations for the Diagnosis and Treatment of HIV-Related Tuberculosis

The presentation of TB varies in HIV-infected patients according to the CD4 cell count [3]:

Early HIV disease (CD4 cells >350): TB has a similar presentation to HIV-negative patients:

- Extrapulmonary TB disease is seen in approximately 25% of patients
- Positive tuberculin skin test (PPD) is common (~85%)
- Chest radiograph findings:

  Upper lobe predominance
  Cavitary lesions
  Pleural disease

  Advanced HIV disease (CD4 T-cells <200):

- Extrapulmonary TB disease is common (~60%)
- Positive TST <50% (could be because of anergy)
- Chest radiograph findings:

  Lower and middle lobe infiltrates
  Paratracheal and hilar adenopathy
  Pleural and pericardial involvement
  Patients who have CD4 T-cells between 200 and 350 have variable presentations

Considerations for TB Therapy for HIV-Infected Patients Treated With Antiretroviral Therapy

All HIV-infected patients with active TB should be started on ART. For patients with <200 CD4 cells, it is recommended that ART be initiated within 2–4 weeks of

starting TB treatment. For patients with CD4 count 200–500 cells/mm^3, guidelines recommend the initiation of ART within 2–4 weeks, or at least by 8 weeks after the start of TB therapy. For patients with CD4 count >500 cells/mm^3, it is recommended to start ART within 8 weeks of TB therapy [3, 4].

Drug Interactions Between Rifamycins for TB and Antiretroviral Therapy for HIV

The management of HIV + TB coinfection is complicated by potential drug interactions between rifamycins and ART. Rifampin induces the activity of cytochrome P450 (CYP) system, specifically the isoenzyme CYP3A4, and may decrease serum concentrations of ART. Despite pharmacokinetic drug interactions, a rifamycin should be included in regimens for patients receiving ART, with dosage adjustment if necessary. The Centers for Disease Control and Prevention (CDC) guidelines list as a preferred regimen efavirenz-based ART with rifampin-based TB treatment. If a PI-based regimen is used, rifabutin is the preferred rifamycin [5].

Latent TB Infection (LTBI) and Missed Opportunity for Prevention

One year prior to admission, the patient lived with his brother who was diagnosed with pulmonary TB. However, the patient did not have a medical evaluation or treatment for LTBI or offered HIV testing. It is likely that his current TB disease could have been prevented with treatment for LTBI with isoniazid for 9 months.

Case 2

Keywords Miliary TB, Corticosteroids, Anti-tumor necrosis factor agonists, Interferon gamma release assays

A 36-year-old female from Guatemala with systemic lupus erythematosus (SLE) came to the rheumatology clinic for an unscheduled visit looking very ill in February 2008. She had a swollen left knee and fever for 2 weeks. She also had a lesion on her upper lip. The patient was most recently placed on high dose prednisone 60 mg daily for the past 2 months to control symptoms of arthritis and fever. She was previously on prednisone 15 mg daily for 4 months. She had four hospital admissions during the past 6 months for worsening of symptoms of SLE and was previously treated with methotrexate. She also had a history of myositis. The patient was diagnosed with SLE in 2004.

Past Medical History

Her past surgical history was significant for a cholecystectomy and three cesarean sections. Her tuberculin skin test (PPD) was negative in 2007. She received the BCG vaccine in 1971.

Social and Environmental History

She did not smoke, drink, or use IV drugs. She was separated from her husband and was unemployed. She lived with her three children in an apartment and had no recent travel. She has lived in the United States for 5 years.

Review of Systems

The patient had arthritis and fever. Her left knee was painful and swollen. She also described feelings of fatigue and depression.

Allergies

No known allergies

Medications

Prednisone 60 mg daily, Plaquenil 200 mg daily

Physical Examination

She was a well-developed female who appeared in moderate distress. Vitals: Temperature: 101.8°F, pulse: 118, RR: 20, BP: 112/57. HEENT: The examination revealed facial hyperpigmentation associated with nasolabial and periorbital sparing. There were two verrucous lesions, 5 cm and 1 cm on her upper lip, with no bleeding or exudates. Her heart sounds were regular with no heart murmur. Her lungs were clear. Extremities: Her left knee was swollen and tender to palpation. There was moderate warmth and erythema with limited range of motion. She had a BCG scar on her right shoulder.

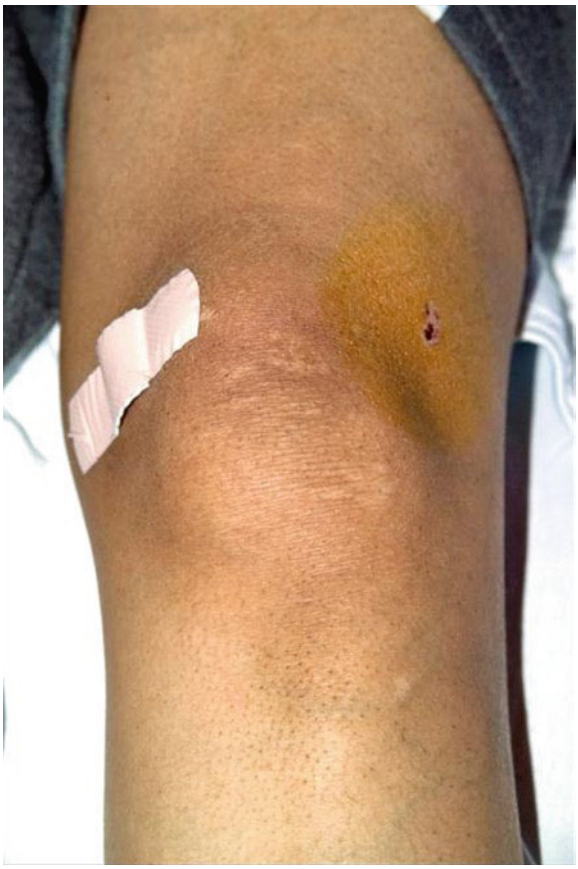

Fig. 8.2 Left knee after aspiration

The left knee was aspirated in the rheumatology clinic and the patient was admitted to the hospital (Fig. 8.2).

Diagnostic Testing

Laboratory Data

Hematology: WBC 8.6 (3.7–10.3) K/mm^3, Differential 79.2 neutrophils, no bands, Hb 12.3 (11.8–14.7) g/dL, Hct 37.9 (36.0–44.0)%, Platelets 425 (150–350) K/mm^3

Chemistry: Na 135 (135–145) mmol/L, K 3.6 (3.5–5.1) mmol/L, Cl 95 (100–110) mmol/L, HCO_2 26 (20–30) mmol/L, Glucose 164 (65–99) mmol/L, AST 50 (10–40) U/L, ALT 29 (5–40) U/L, alkaline phosphatase 88 (30–100) U/L, total bilirubin 0.3 (0.0–1.0) mg/dL, total protein 7.4 (6.0–8.0) g/dL, albumin 3.2 (3.5–5.0) g/dL

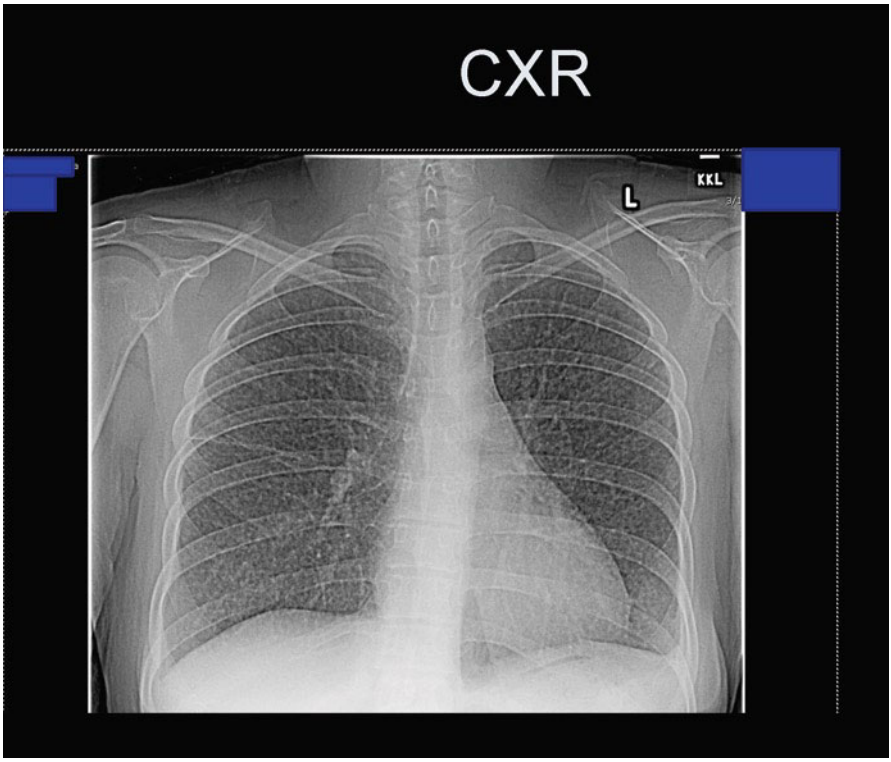

Fig. 8.3 Chest radiograph

Left Knee Synovial Fluid

Color: Pale yellow, moderately cloudy, WBC 27,500 (<200/mm^3), Crystals: none, Neutrophils 73%, Lymphocytes 11%, Mono/Histiocytes 16%, 3+ PMNs, 1+ Monos, No organisms on Gram stain, AFB smear negative, India ink negative.

Chest radiograph: 2/29/2008 (see Fig. 8.3)

There were diffuse innumerable pulmonary nodules, most of which were miliary in size. This is a new finding when compared with the prior exam on 10/22/2007. There has been interval decrease or resolution of the previously noted left pleural effusion. Impression: Diffuse pulmonary nodules, likely represents hematogenous infection or hematogenous metastasis.

Serologic studies: HIV negative, Hepatitis BS Antigen negative, Hepatitis C negative, ANA positive 1:1,280 (negative), speckled pattern, Anti-DS-DNA, SCR negative

C3: 124 (90–180), C4: 35.6 (10–40) mg/dL

Tuberculin skin test (PPD): negative

Microbiology:

Sputum for AFB negative × 3

With Presented Data, What Is Your Working Diagnosis?

The differential diagnosis for the left knee joint effusion would include SLE, rheumatoid arthritis, gout, pseudogout, and infection. The causes of a septic joint would include *Staphylococcus aureus*, *Streptococcus pneumonia*, *Neisseria gonorrhoeae,* and *Brucella*. Other infectious diseases such as tuberculosis and coccidioidomycosis would also be of concern particularly in a patient on immunosuppressive therapy. The cell count in the synovial fluid (WBC 27,500: polys 73%, lymphocytes 11%, mono/histiocytes 16%) seems to suggest more of an inflammatory process (WBC count of 2,000–75,000 (>50% polys) related to SLE. A septic joint usually has >50,000 WBCs (>75% polys) often with a positive Gram stain. A synovial biopsy might be helpful if the synovial fluid cultures are negative.

The chest radiograph on admission showed a miliary pattern which was not present in the previous film from the previous year. The differential diagnosis includes community-acquired pneumonia (CAP) – specifically atypical pneumonia (*Mycoplasma, Chlamydia pneumoniae, Legionella*), TB, fungal infections (coccidioidomycosis, cryptococcosis, histoplasmosis, blastomycosis), *Pneumocystis jirovecii* pneumonia (PCP), sarcoidosis, lymphoma, and methotrexate drug-induced pneumonitis. The lip lesion could be caused by SLE or fungal infections. Hyperpigmentaion of the face could be a malar rash from SLE. Hyperpigmentation could also be related to adrenal insufficiency from disseminated histoplasmosis or TB. The miliary pattern of the chest radiograph favors a diagnosis of TB or fungal disease, which could also account for the left knee effusion.

Workup

Blood cultures × 2 were negative for bacteria.
Blood cultures × 1 were negative for fungus.
Synovial fluid cultures: Bacteria: negative, Fungus: negative, *M. tuberculosis*: negative.
Punch biopsy of left upper lip lesion: Benign squamous epithelium with ulceration and viral cytopathic changes consistent with herpes. GMS stain is negative for fungal elements. Immunostatin for HSVI is positive. Dermatology consult: Herpes simplex virus mucocutaneous lesion. Acyclovir was recommended.
Interferon gamma release assay: T-Spot. *TB* assay was positive (ESAT-6>20, CFP-10>20).
A bronchoscopy was scheduled.

What Is Your Diagnosis and Why?

The chest radiograph showed diffuse, bilateral infiltrates with a nodular appearance consistent with a miliary pattern in both the upper and lower lung fields. The term

miliary is used to describe the appearance of the small white nodules which is similar to millet grain seeds. Miliary TB often occurs when a massive MTB bacteremia causes diseases in several organs. Many patients present with fever of unknown origin, weight loss, and fatigue. At least 30% of children with miliary disease have a negative tuberculin skin test (TST). Clinical manifestations depend on the number and location of the disseminated organism. Sputum AFB smears are often negative in miliary TB.

Patients with cavitary lesions on chest radiographs are more likely to have positive AFB smears. Even though the AFB smear was reported as negative, the culture may still be positive and MTB may still be isolated. If the index of suspicion is still high for tuberculosis, then the patient should be managed as if they have TB regardless of the negative smear results [6].

We elected to send an interferon gamma release assay (T-Spot) since the tuberculin skin test was negative. T-Spot is a blood test which aids in the detection of tuberculosis infection. The positive result from the T-Spot assay gave us additional evidence that this might be MTB infection, which is often difficult to diagnose in an immunocompromised patient. Based on the history, abnormal chest radiograph and positive T-Spot assay, a four-drug regimen of isoniazid, rifampin, pyrazinamide, and ethambutol was initiated. The rheumatology consult recommended reducing the prednisone since this did not appear to be a lupus flare. The diagnosis of TB was confirmed by a bronchoscopy. The bronchial alveolar lavage (BAL) sample from the right middle lobe was AFB smear positive and grew MTB. The three induced sputum samples which were AFB smear negative also subsequently grew MTB. The susceptibility testing confirmed a pan-sensitive organism. Although blood cultures were not sent for TB cultures, a stool sample was obtained on TB treatment and was AFB smear positive, but MTB culture negative. The joint fluid also did not grow MTB. The left knee effusion might have been from SLE. The effusion did not recur after drainage.

The patient was discharged on tuberculosis medications: rifampin 600 mg, isoniazid 300 mg, pyrazinamide 1,500 mg, ethambutol 1,200 mg, and pyridoxine (vitamin B6) 200 mg daily. She was continued on prednisone 15 mg in the morning and 5 mg at night, plaquenil 200 mg daily, and acyclovir 200 mg 5 × day.

The public health department initiated contact investigation and screened her three children at home. The TSTs were negative at baseline and also negative when repeated in 3 months. There was no documented transmission of TB to the children in the home.

The patient's previous TST in 2007 was negative. Many immunocompromised patients with LTBI have negative TSTs. More innovative tests are needed to diagnose LTBI in immunocompromised patients.

Discussion

The diagnosis of TB is challenging in immunocompromised patients. While HIV infection is the greatest risk factor for the progression of LTBI to active TB, patients with LTBI on immunuosuppressive therapy are also at high risk. Prednisone (or its

equivalent) given >15 mg/day for 2–4 weeks suppresses tuberculin reactivity and could cause the reactivation of TB [7].

Newer medications to treat autoimmune diseases have also given rise to concerns about the risk of tuberculosis. Rheumatoid arthritis is an autoimmune disease in which the body's defense system is abnormally regulated, eventually causing joint destruction and debility in those with insufficient treatment. Huge strides in the advent of newer medications have transformed the prognosis of this disease for the better, and now we are seeing much less debility.

The standard of care in patients with aggressive rheumatoid arthritis is trending toward aggressive treatment, particularly geared to the use of anti-tumor necrosis factor (TNF) alpha agents: infliximab (Remicade), etanercept (Enbrel), and adalimumab (Humira). These medications work by blocking TNF alpha, an inflammatory cytokine, and are approved for treating rheumatoid arthritis and other selected autoimmune diseases. The data is overwhelming in the success of improvement in patients' overall quality of life. While we are impressed with the success of these medicines, there are drawbacks that cannot be ignored. As these medicines modulate immunity, there is an association of anti-TNF alpha treatment with reactivation tuberculosis, in which quiescent tuberculosis bacilli are awakened by the elimination of that which suppresses their activity [8, 9].

Screening for LTBI has become a main topic of interest in the field of rheumatoid arthritis. To date, there is no gold standard for detecting LTBI. Most countries at this time have positions on the screening of LTBI in patients prior to the administration of anti-TNF alpha agents.

The TST is the current method to detect LTBI. There is no doubt that the use of the TST in screening for LTBI is essential, especially in high TB exposure populations. However, the TST does have glaring drawbacks, among which are follow-up and both false positives and negatives. Limitations include the need for at least two patient contacts, uncertainty about the immune status of the person tested, false-positive results because of cross-reactivity with BCG vaccine and NTM, technical difficulties in administering the test, and errors related to subjectivity in reading the results. Consequences range from unnecessary toxicity from TB medications to reactivation TB in patients who failed to be identified as LTBI subjects.

Guidelines for Interpretation of the TST for the Treatment of LTBI [7]

For persons who are at highest risk for developing active TB if they are infected with *M. tuberculosis*:

≥5 mm induration

- HIV infection
- Organ transplants and those conditions that require prolonged use of corticosteroids (the equivalent of prednisone >15 mg daily for 1 month or more) or other immunosuppressive agents such as TNF-antagonists
- Close contacts of active TB
- Abnormal chest radiographs with fibrosis consistent with prior TB

For persons with an increased probability of recent infection or with other clinical conditions that increase the risk for progression to active TB:

≥10 mm of induration is considered positive

- Recent immigrants (i.e., within the last 5 year) from high prevalence countries
- Injection drug users
- Residents and employees of high-risk congregate settings (including health care workers with exposure to TB)
- Mycobacteriology laboratory personnel
- Persons with clinical conditions such as silicosis, diabetes mellitus, chronic renal failure, leukemias and lymphomas, carcinoma of the head, neck, or lung, weight loss of 10% ideal body weight, gastrectomy, and jejunoileal bypass
- Children younger than 4 years of age

For persons at low risk for TB, for whom tuberculin testing is not generally indicated, ≥15 mm of induration is considered positive.

Interferon gamma release assays (IGRAs) are blood tests which detect the release of gamma interferon by T-cells after exposure to specific TB antigens (culture fibrate protein (CFP-10) and early secretory antigen target (ESAT-6). The T-cells of individuals previously exposed to tuberculous antigens produce interferon-gamma when reexposed to these mycobacterial antigens [10].

The U.S. Food and Drug Administration (FDA) has approved the use of three IGRAs:

- QuantiFERON®-TB Gold test (QFT-G)
- QuantiFERON®-TB Gold-in-Tube test (QFT-GIT)
- T.SPOT®*TB* test (T-Spot)

The Centers for Disease Control and Prevention (CDC) recommends that IGRAs can be used in most circumstances in which the tuberculin skin test (TST) is currently used. Compared with the TST, IGRAs are less likely to be positive following BCG vaccination and infections with NTM. IGRAs also require only a single patient visit. Although routine testing with both a TST and an IGRA is not generally recommended, results from both tests might be useful when the initial test (TST or IGRA) is negative, and the risk of TB is increased (e.g., persons who are immunocompromised), a positive result from a second test increases the sensitivity of detection. However, multiple negative results from any combination of these tests cannot exclude *M. tuberculosis* infection. TSTs and IGRAs (QFT-G, QFT-GIT, and T-Spot) should be used as aids in diagnosing infection with MTB [10]. Our patient had a negative TST and positive T-Spot. The diagnosis of active TB was confirmed by positive MTB cultures.

Questions

Case 1

1. Which is the greatest risk factor for the progression of LTBI to active TB?

   (a) HIV infection
   (b) Diabetes
   (c) Obesity
   (d) Silicosis
   (e) Malnutrition

2. Which of the following medications interacts most frequently with protease inhibitors used to treat HIV infection?

   (a) Ethambutol
   (b) Rifampin
   (c) Isoniazid
   (d) Pyrazinamide
   (e) Pyridoxine

3. Which of the following HIV antiretroviral medications is preferable for use in a patient who is also taking rifampin 600 mg daily?

   (a) Lopinavir (Kaletra)
   (b) Darunavir (Prezista)
   (c) Atazanavir (Reyataz)
   (d) Efavirenz (Sustiva)
   (e) None of the above

4. The Immune Reconstitution Inflammatory Syndrome (IRIS) has been reported to occur in HIV-positive patients with which of the following?

   (a) Disseminated tuberculosis
   (b) *Mycobacterium avium* complex lymphadenitis
   (c) Cytomegalovirus (CMV) retinitis
   (d) Cryptococcal meningitis
   (e) All of the above

5. Which of the following are associated with the Immune Reconstitution Inflammatory Syndrome (IRIS) in patients coinfected with HIV and tuberculosis?

   (a) Low CD4 cells
   (b) High viral load prior to the initiation of antiretroviral therapy
   (c) Mean onset of symptoms in 2 weeks after the initiation of antiretroviral therapy
   (d) Fever and lymphadenopathy
   (e) All of the above

Case 2

6. A 36-year-old woman with rheumatoid arthritis is being screened prior to starting therapy with a TNF antagonist (Remicade). She has a tuberculin skin test with 6 mm of induration which she believes is from the BCG vaccine she received as a child. All of the following would be reasonable except:

   (a) Send an interferon gamma release assay, such as QuantiFERON-Gold or T-Spot, for additional evidence to convince her that this is from tuberculosis infection
   (b) Prescribe 9 months of isoniazid
   (c) Repeat the tuberculin skin test (PPD) to detect a boost to 16 mm
   (d) Obtain CXR to rule out active disease
   (e) Inquire about symptoms of cough and fever

7. Which of the following tests is a blood test to identify patients who have been infected with *M. tuberculosis*?

   (a) Mantoux test (PPD)
   (b) Nucleic acid amplification test
   (c) Smear for acid-fast bacilli (AFB)
   (d) Interferon gamma release assays (QuantiFERON®-TB Gold and T-SPOT®*TB*)
   (e) Drug susceptibility test

8. Which finding on a chest radiograph is more likely to yield sputum positive for acid fact bacilli (AFB) in a patient with tuberculosis?

   (a) Cavitary lesion
   (b) Pleural effusion
   (c) Hilar lymph node enlargement
   (d) Miliary infiltrate
   (e) Lower lobe infiltrate

9. A tuberculin skin test (PPD) reaction of 5 mm rather than 10 mm is considered positive in which of the following risk factors for TB?

   (a) Diabetes
   (b) Conditions that require prolonged use of corticosteroids or other immunosuppressive agents such as TNF-antagonists
   (c) Silicosis
   (d) Chronic renal failure
   (e) All of the above

10. Which is true about the TST (PPD) and interferon gamma release assays (IGRAs)?

    (a) TSTs and IGRAs (QFT-G, QFT-GIT, and T-Spot) should be used as aids in diagnosing infection with MTB
    (b) IGRAs offer enhanced specificity in populations previously vaccinated with BCG
    (c) A negative IGRA as well as a negative TST may not be sufficient to exclude a diagnosis of MTB infection
    (d) As with the TST, IGRAs generally should not be used for testing persons who have a low risk for both infection and progression to active TB if infected (except for those likely to be at increased risk in the future)
    (e) All of the above statements are true

Answer key: 1. (a), 2. (b), 3. (d), 4. (e), 5. (e), 6. (c), 7. (d), 8. (a), 9. (b), 10. (e)

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Part IV
Obstructive Lung Diseases

Chapter 9
Asthma

Neil Baman and Timothy J. Craig

Abstract Asthma is a common chronic inflammatory disorder of the airways, characterized by paroxysmal narrowing of the bronchial airways due to inflammation of the bronchi and contraction of the bronchial smooth muscle. Common clinical manifestations include wheezing, coughing, shortness of breath, and chest tightness. Prognosis is generally good with proper control of asthma with step-down therapy. However, recognition of atypical presentations of asthma is vital in any clinical practice in order to improve patient outcomes.

Keywords Asthma • Refractory asthma • Airway obstruction • Spirometry • Allergic asthma • Asthma treatment • Bronchial hyperresponsiveness

Case 1

A 13-year-old male is referred for suboptimally controlled asthma. He states that he has had this throughout his entire life, reporting one hospitalization at the age of 2. Following that he reports only one trip to the emergency department at the age of 4. He states that he was not intubated during that hospitalization. He has had no further visits to the emergency department since the age of 4.

In regards to his current symptoms, he reports that he has to use his rescue albuterol inhaler approximately 2–3 times on a weekly basis, primarily for wheezing or shortness of breath. This is in addition to using his albuterol inhaler prior to exercise or prior to gym class. In addition, he is having nocturnal symptoms twice weekly where he would wake up at nighttime short of breath and reaching for

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albuterol inhaler. He states that this has been ongoing over the course of several years. Currently, he is on an extensive regimen that consists of fluticasone/salmeterol 115/21 mcg two puffs inhaled b.i.d. He also has albuterol to be used as needed. In the past, he has tried montelukast, but this led to neuropsychiatric side effects. He does check his peak flows on a regular basis and does pertain to an asthma action plan. It appeared that his best peak flow reading was around 300. Typically, his baseline peak flows range from 150 to 250. Other known triggers of his exacerbations include viral upper respiratory infections.

Physical examination revealed evidence of swollen inferior turbinates bilaterally but no evidence of purulent drainage, nasal polyposis, nor sinus tenderness. Posterior oropharynx revealed no evidence of cobblestoning nor candidiasis. Lung fields were clear to auscultation with no evidence of wheezes, rales, nor ronchi. No murmurs could be auscultated. There was no evidence of peripheral edema, cyanosis, cobblestoning, norskin rashes or lesions.

With the Presented Data, What Is Your Working Diagnosis?

The first step in dealing with an asthma patient is to make sure it is asthma. Although many cases of recurrent cough and wheezing in children and adults are due to asthma, other conditions are often misdiagnosed as asthma. The younger the child, the more the need to exclude underlying disease at an early stage. The differential diagnosis of children with frequent respiratory infection and wheezing should include:

- Bronchitis
- Cystic fibrosis
- Pneumonia/bronchiolitis
- Allergic rhinitis and sinusitis
- Bronchopulmonary dysplasia (in premature infants)
- Vascular rings or laryngeal webs
- Alpha-1-antitrypsin deficiency
- Vocal cord dysfunction
- Airway obstruction with a foreign body
- Aspiration from swallowing mechanism dysfunction or gastroesophageal reflux
- Dysmotile cilia syndrome
- Heart disease
- Immunodeficiencies

What Tests or Treatment Would You Recommend Next?

A detailed process of history taking, physical examination, and diagnostic studies establishes the diagnosis of asthma in the majority of cases. Spirometry is the preferred method of diagnosis of airflow obstruction. Significant reversibility is

indicated by an increase in FEV1 of ≥12% from baseline after administration of a short-acting bronchodilator. Alternative ancillary studies to support the diagnosis of asthma and to rule out other disorders include bronchoprovocation testing with methacholine, radiographic imaging of the chest, sweat chloride testing, and allergy testing. Methacholine challenges are useful in patients who have symptoms suggestive of asthma, unremarkable spirometry, and a lack of response to asthma therapy. Although not routinely recommended, chest radiographs may be useful to display findings consistent with asthma, such as hyperinflation, peribronchial thickening, and mucoid impaction with atelectasis; findings suggestive of congenital malformations (e.g., a right aortic arch suggestive of a vascular ring); or evidence of airspace disease consistent with aspiration or cystic fibrosis. A negative sweat chloride test reduces the likelihood of the diagnosis of cystic fibrosis in children. Finally, allergy testing via skin prick testing or serum-specific IgE testing is beneficial to recognize potential triggers of asthma.

Final Diagnosis

Severe Persistent Allergic Asthma

In this case, spirometry was performed in the office, revealing an FVC of 2.79 (98% of predicted), FEV1 of 2.05 (81% of predicted), FEV1/FVC ratio of 73%, FEF 25–75% of 1.55 (48% of predicted), and PEFR of 4.39 (79% of predicted). This revealed evidence of obstructive pulmonary impairment. After bronchodilator therapy, his FEV1 increased to 2.48, representing a 16% increase and significant reversibility.

In addition, allergy testing to common aeroallergens via skin prick testing was performed with a positive histamine control and a negative diluent control. The patient exhibited positive results to several tree pollens, dust mite, cat dander, and dog dander.

Given the patient's diagnosis of severe persistent allergic asthma, treatment was targeted at antigen avoidance and maximizing his asthma regimen. Animal dander avoidance measures, including the use of high-efficiency particular air (HEPA) filters and aggressive cleaning were initiated. In addition, dust mite avoidance measures of utilizing physical barriers and regulating humidity were also discussed with the patient. Furthermore, the dose of the patient's inhaled glucocorticoid was increased in conjunction with establishing an asthma action plan and use of an AeroChamber® to assist delivery of medicine to the small airways in the lungs. Finally, due to the persistence of symptoms related to his asthma, the patient was started on subcutaneous immunotherapy, targeting tree pollens, dust mite, cat dander, and dog dander. A recent addition to the National Asthma Education and Prevention Program guidelines for asthma management in 2007, allergen immunotherapy is recommended as an adjunct to standard pharmacotherapy [1]. The patient tolerated the immunotherapy without difficulty and his asthma is now optimally controlled.

Assessing for allergic sensitivity to inhaled allergens begins with history taking. If a patient reports that exposure to typical allergens causes asthmatic symptoms, then positive allergy tests will have a greater positive predictive value. The most sensitive way to identify potentially relevant allergens is by appropriate allergy skin testing. Because allergen avoidance is so important in asthma management, it is usually recommended that any asthmatic who wheezes more than 2 days per week be skin tested. Given the fact that the majority of symptoms manifested in patients with allergic and nonallergic asthma are the same (coughing, wheezing, shortness of breath or rapid breathing, and chest tightness), one must consider this diagnosis in any individual diagnosed with asthma. While both types of asthma manifest the same symptoms, the difference is made by the trigger of these symptoms. Patients with allergic asthma, as suggested by seasonal exacerbations or allergen-related triggering events, may be sensitive to tiny amounts of aeroallergens (e.g. house dust mite antigen, cat and dog danders, cockroach antigen, pollens, and mold spores). This is why all asthma sufferers need to be aware of their type of asthma, so they can apply preventive and avoidance measures if possible.

Nearly 5 million asthma sufferers are under age 18. It is the most common chronic childhood disease, affecting more than 1 child in 20. Many children wheeze and cough early in life. However, the major challenge for any clinician is to differentiate children with transient symptoms from children who will have chronic asthma. One study revealed that only 10% of children who received asthma medication in the first year of life were still using this medication 3 years later [2]. In addition, approximately 33% of children under the age of 3 had wheezing with associated respiratory illnesses but almost 60% of these children had complete resolution of wheezing by the age of 6 [3]. So which children with recurrent wheezing will develop asthma by school age? Multiple asthma predictive indices have been proposed but the only one that has been tested in independent studies and different populations is the asthma predictive index (API). Using data from 1,246 children in the Tucson Children's Respiratory Study birth cohort, the API uses factors that are found during the first 3 years of life to predict continued wheezing at school age. A positive API score requires recurrent episodes of wheezing during the first 3 years of life and 1 of 2 major criteria (physician-diagnosed eczema or parental asthma) or 2 of 3 minor criteria (physician-diagnosed allergic rhinitis, wheezing without colds, or peripheral eosinophilia ≥4%) (see Table 9.1) [4]. With excellent negative predictive values, the API is useful to rule out the likelihood of asthma by school age in young children with wheezing. For children who are "early wheezers during the first 3 years of life," API negative predictive values ranged from 93.9% at 6 years of age to 86.5% at 13 years of age. For children who are "early frequent wheezers during the first 3 years of life," the negative predictive values were 91.6% and 84.2% for 6 and 13 years of age, respectively [5].

In a typical individual, lung function increases throughout childhood, levels off between the ages of 25 and 35, and then declines after the age of 35 years at a rate of 22 mL/year [6]. However, in subjects with asthma, the decline in FEV1 is 38 mL/year [7].

Table 9.1 Major and minor criteria for the asthma predictive index (API)

Major criteria:
- Physician-diagnosed parental asthma
- Physician-diagnosed eczema

Minor criteria:
- Physician-diagnosed allergic rhinitis
- Wheezing without colds
- Peripheral eosinophilia ≥ 4%

A positive API score requires recurrent episodes of wheezing during the first 3 years of life and 1 of 2 major criteria (physician-diagnosed eczema or parental asthma) or 2 of 3 minor criteria

Case 2

A 36-year-old female with asthma is referred for suboptimally controlled asthma for approximately 5 years. Her chief complaint is primarily dyspnea with minimal exertion and with viral upper respiratory infections. She was originally diagnosed with asthma at the age of 16 years. Prior to this age, she reports no signs or symptoms that were consistent with asthma or any other pulmonary-related process. Family history is significant for late-onset asthma in her father. Social and environmental history did not reveal any occupational exposures nor exposure to tobacco smoke. She does have a cockatiel at home but she cannot clarify if her symptoms are worse around the bird.

Upon further questioning, she has been hospitalized for asthma exacerbations on five separate occasions but did not require intubation. She requires an oral prednisone course for asthma about once every 6 months. Recently within the past 2 months, she was hospitalized to an academic center for status asthmaticus. She was on continuous nebs and required corticosteroid burst as well. She was discharged on a prednisone taper, fluticasone–salmeterol 500 mcg/50 mcg one inhalation twice daily, montelukast 10 mg daily, and albuterol as needed. Prior to the recent hospitalization she has been on fluticasone–salmeterol and montelukast, but she ran out of the medications about a week prior to worsening of her asthma symptoms. She did not have an asthma action plan. She does check her peak flow at home which averages between 350 and 400. Today she reports that she has been doing much better, denying chronic cough, shortness of breath, wheezing, nocturnal symptoms or restriction of physical activities.

Physical examination revealed no evidence of swollen turbinates, nasal polyposis, nor sinus tenderness. Posterior oropharynx revealed no evidence of cobblestoning nor candidiasis. Lung fields were clear to auscultation and revealed no evidence of wheezes, rales, nor ronchi. No murmurs could be auscultated. There was no evidence of peripheral edema, cyanosis, cobblestoning, norskin rashes, or lesions.

Pulmonary function tests pre- and postbronchodilator were performed at this visit, which revealed FVC 2.71 L (66% of predicted), FEV1 2.06 L (61% of predicted),

FEV1/FVC ratio of 0.76, and FEF 25–75% (59% of predicted). The flow-volume loop was normal in appearance. There was no significant reversibility after bronchodilator therapy with the exception of a 13% change in the FEF 25–75%. Carbon monoxide diffusing capacity (DLCO) was 74% of predicted. Chest X-ray was normal in appearance. There was no record of serum-specific IgE testing or total serum IgE level.

With the Presented Data, What Is Your Working Diagnosis?

The differential diagnosis in this patient with obstructive findings on spirometry includes asthma and diseases that mimic severe asthma. Vocal cord dysfunction, also known as paradoxical vocal cord motion, is the most common masquerader of severe asthma. Chronic obstructive pulmonary disease (COPD) is unlikely due to the lack of smoking history. Central airway obstruction from tracheal strictures (e.g., from prior intubation), tracheal compression by goiter, tracheal and proximal bronchial tumors, and vascular rings can be considered but is also unlikely due to the normal appearance of her flow-volume loops. In the setting of her exposure to birds, hypersensitivity pneumonitis should also be considered. Other unlikely causes include Churg–Strauss syndrome, cardiac disease, sarcoidosis, chronic pulmonary infections, alpha-1-antitrypsin deficiency, allergic bronchopulmonary aspergillosis, and bronchiectasis.

What Tests or Treatment Would You Recommend Next?

Old medical records and a high-resolution chest CT scan to evaluate for reticular, nodular, ground glass opacities, or bronchiectasis were ordered. In addition to a total IgE, serum-specific IgE testing for different environmental and occupational aeroallergens can be considered. A methacholine challenge test would be appropriate if asthma was in doubt. An echocardiogram to evaluate for heart dysfunction is reasonable. Bronchoscopy with bronchoalveolar lavage can also be considered in the future depending on the above results.

Final Diagnosis

1. Hypersensitivity pneumonitis
2. Severe persistent asthma

A high-resolution chest CT revealed ground glass opacities. In the setting of these findings and history of appropriate exposure, a bronchoalveolar lavage was performed revealing a low CD4 to CD8 ratio, consistent with the diagnosis of hypersensitivity pneumonitis, also known as bird fancier's lung. Treatment was

targeted at antigen avoidance, glucocorticoid therapy, and maximizing her asthma regimen. However, in cases similar to this, recovery is not assured because high levels of bird antigens can be detected in the home environment for prolonged periods of time after bird removal and environmental cleanup.

Due to the symptomatic nature of the patient, removal of the bird from her home was strongly recommended. In addition, she was initiated on prednisone, where 60 mg daily dose was maintained for 1 week and then tapered over the next 4 weeks. Studies have shown that acceleration of recovery is seen with glucocorticoids, particularly in severely ill patients; however, the long-term outcome appears unchanged by glucocorticoid treatment.

From an asthma standpoint, her medication regimen was changed to fluticasone 230 mcg/salmeterol 21 mcg HFA two puffs inhaled with the use of an AeroChamber® to assist delivery of medicine to the small airways in the lungs. In addition, proper technique was demostrated and observed and an asthma action plan was formulated. She returned 4 weeks later and reported better breathing during her course of prednisone. Her peak flows increased significantly and she coughed and wheezed much less. Follow-up 3 months later off of prednisone revealed significant improvement in her symptoms.

The key to this case is to recognize pertinent environmental exposures that may contribute to progressively worsening asthma. The patient's pulmonary function tests are not typical of solely asthma. A complex syndrome representing an immunologic reaction to an inhaled agent occurring within the pulmonary parenchyma, hypersensitivity pneumonitis, has numerous inciting agents, including various occupational exposures and excrement on dried, finely dispersed dust from pigeons and other birds and fowl.

Case 3

Our final patient is a pleasant 24-year-old female with a past medical history of asthma and gastroesophageal reflux disease who presents to the office a second opinion. She is frustrated by her significant daily cough and continued phlegm production. Cough is usually productive of white foamy sputum. She has occasional spells of sustained coughing when she loses her breath. These coughing spells can be triggered by odor, atmosphere changes, tobacco smoke, stress, wood burning, cats, dogs, talking, or eating. She also reports shortness of breath at baseline. She has been taking her montelukast regularly and budesonide/formoterol 160/4.5 mcg two puffs twice daily with an AeroChamber®; however she has been taking her nebulizer frequently in the mornings as a "preventive" medication. She also uses her albuterol more than 5 times per week.

In regard to her reflux, she currently is on omeprazole 20 mg daily and continues to have occasional acidic burping and coughing with eating. Her omeprazole was recently initiated and she is unsure whether it has improved her symptoms as of yet. She has no dysphagia.

Physical examination revealed no evidence of swollen turbinates, nasal polyposis, nor sinus tenderness. Posterior oropharynx revealed no evidence of cobblestoning nor candidiasis. Lung fields were clear to auscultation and revealed no evidence of wheezes, rales, nor ronchi. No murmurs could be auscultated. There was no evidence of peripheral edema, cyanosis, cobblestoning, norskin rashes, or lesions.

Pulmonary function testing revealed an FVC of 2.59 (68% of predicted), FEV1 1.79 (60%), FEV1/FVC 69%, FEF 25–75% of 1.16 (40%), and PEFR 5.1 (72%). There is mild flattening of the inspiratory loop. She was given four puffs of albuterol and her postbronchodilator spirometry revealed FVC 2.78 (73%), representing a 7% change; FEV1 2.07 (69%), which is a 15% change; FEV1/FVC 74%, which is an 8% change; FEF 25–75% of 1.56 (54%), which is a 35% change; PEFR 6.06 (86%), which is a 19% change.

With the Presented Data, What Is Your Working Diagnosis?

The differential diagnosis in this patient with obstructive findings on spirometry includes asthma and diseases that mimic severe asthma. Given the flattening of the inspiratory loop, disease processes involving a variable extrathoracic airway obstruction should be considered (see Fig. 9.1). This would include vocal cord dysfunction, also known as paradoxical vocal cord motion. Patients with paradoxical vocal cord motion disorder are often misdiagnosed with asthma, because the sound produced can be mistaken for asthmatic wheezing. Other disorders involving extrathoracic airway obstruction include tracheomalacia, vocal cord paralysis, and vocal cord polyps. Meanwhile, variable intrathoracic airway obstruction is associated with tracheomalacia of the intrathoracic airway, tumors, and mediastinal adenopathy; fixed obstruction can be secondary to tracheal tumors, a foreign body, subglottic stenosis (as caused by intubation and Wegener's granulomatosis), and tracheal stenosis (caused by intubation).

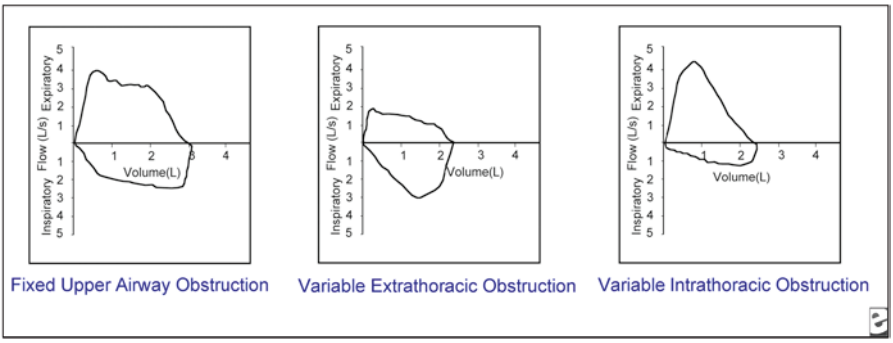

Fig. 9.1 Flow-volume loops involving fixed upper airway obstruction, variable extrathoracic obstruction, and variable intrathoracic obstruction

What Tests or Treatment Would You Recommend Next?

For further evaluation of disease processes involving a variable extrathoracic airway obstruction, a laryngoscopy would be recommended in order to visualize abnormal adduction of the true vocal cords. The gold standard for diagnosing paradoxical vocal cord motion is direct observation with laryngoscopy at the time the patient is having symptoms. Direct visualization of the vocal cords, at the time the patient is free of symptoms, is expected to be normal. Hyperventilation can be used to induce vocal cord changes while the laryngoscope is in place to diagnose the disorder. Chest radiographs can also be utilized to exclude an intrathoracic cause of dyspnea but in this setting, they are generally not helpful. Direct visualization of the vocal cords, at the time the patent is free of symptoms with la raise suspicion of asthma but cannot rule out concurrent paradoxical vocal cord motion. Given the severity of asthma, allergy testing via skin prick testing or serum-specific IgE testing may provide additional benefit by recognizing potential triggers of asthma.

Final Diagnosis

1. Moderate persistent asthma
2. Paradoxical vocal cord motion
3. Gastroesophageal reflux disease

Laryngoscopy revealed abnormal adduction of the true vocal cords in addition to the false vocal cords primarily during inspiration. The glottic aperture was also obliterated except for a posterior diamond-shaped passage, consistent with paradoxical vocal cord motion. In addition to concurrently treating her asthma and gastroesophageal reflux disease, the patient underwent speech therapy maneuvers with the goal of terminating acute attacks of paradoxical vocal cord motion and her symptoms dramatically improved. Over the course of several visits, we were able to step down her asthma therapy to an inhaled glucocorticoid only with the use of a long-acting beta agonist and she is currently leading an excellent quality of life.

The key to this case is to recognize the first question that should be asked when confronting an individual with severe asthma-like symptoms: Does the patient really have asthma? In a study of 1,025 patients with dyspnea published in 1997, researchers found an overall 2.8% prevalence of paradoxical vocal cord motion [8]. In fact, another study found that 56% of the 95 patients fulfilling the criteria for this disorder had coexistent asthma [9]. Paradoxical vocal cord motion affects mainly women between the age of 20 and 40, with the average age of diagnosis occurring at 33 years in adults and a 2:1 female predominance [10]. This disorder has been associated with a wide variety of etiologies, including exercise, neurologic injury, psychiatric disorders and stress, gastroesophageal reflux disease, surgery, and exposure to a

variety of irritants. Clinical features that raise suspicion for paradoxical vocal cord motion include minimal or lack of response to aggressive asthma therapy, triggers of stress, anxiety, or other emotional factors, subjectively more difficulty on inspiration than expiration, or a flattened inspiratory flow-volume loop.

Various treatment modalities have been used for paradoxical vocal cord motion that range from speech therapy exercises to pharmacotherapy. In general, therapies for asthma such as beta adrenergic agents and inhaled glucocorticoids are not beneficial unless there is coexistent asthma. Useful therapies for management include reassurance and speech therapy maneuvers in which the patient focuses on making a soft "s" sounds while exhaling. Other helpful maneuvers during acute attacks include panting and coughing. Benzodiazepines have been used to relieve anxiety and have also shown to be effective in terminating acute attacks. Other therapies with potential benefits include heliox, nebulized lignocaine, hypnosis, biofeedback, continuous positive airway pressure, and inhaled anticholinergics.

Another key to this case is the role that gastroesophageal reflux disease may be playing. Reflux disease has been associated with a variety of extraesophageal manifestations, including bronchospasm, laryngitis, and chronic cough. Multiple studies have shown that 34–89% of asthmatics have gastroesophageal reflux disease (GERD) and that up to 40% of asthmatics have peptic esophagitis [11, 12]. Asthma triggered by reflux is thought to be secondary to aspiration of gastric contents into the lung with consequent bronchospasm or reflux-induced activation of a vagovagal reflex arc from the esophagus to the lung causing bronchoconstriction. Hence, asthmatics with gastroesophageal reflux disease should have adequate control of the reflux symptoms.

Discussion

Characterized by the complex interaction of airflow obstruction, bronchial hyperresponsiveness, and underlying inflammation, asthma is a complex chronic condition that is estimated to affect 7% of Americans currently [13, 14]. As per a recent estimate, as many as 300 million people are affected worldwide and 20 million individuals within the United States [1]. In addition, the prevalence of asthma has been increasing since the early 1980s across all age, sex, and racial groups.

Also known as extrinsic asthma, allergic asthma is characterized by symptoms that are triggered by an allergic reaction. As the most common form of asthma, allergic asthma affects over 50% of the 20 million asthma sufferers. In addition, over 2.5 million children under age 18 suffer from allergic asthma. Therefore, allergic asthma should always be considered in an individual with suboptimal control of his asthma. In addition, one must confirm the diagnosis of asthma as many conditions can easily mimic asthma. Finally, consideration toward other disease processes such as paradoxical vocal cord motion and gastroesophageal reflux disease as certain disorders often coexist with asthma and must be treated accordingly.

One must acknowledge that there is currently no cure for asthma, and no single exact cause has been identified. Therefore, understanding the aforementioned issues can certainly empower patients and physicians alike to better gain control of asthma.

Questions

1. A positive asthma predictive index score requires recurrent episodes of wheezing during the first 3 years of life and 1 of 2 major criteria or 2 of 3 minor criteria. Which of the following is *not* part of the major or minor criteria?

   (a) Physician-diagnosed eczema
   (b) Parental asthma
   (c) Physician-diagnosis allergic rhinitis
   (d) Wheezing without colds
   (e) Peripheral eosinophilia ≥8%

2. In a patient with symptoms suggestive of asthma, chest radiographs may be useful to display:

   (a) Findings consistent with asthma, such as hyperinflation, peribronchial thickening, and mucoid impaction with atelectasis
   (b) Findings suggestive of congenital malformations (e.g., a right aortic arch suggestive of a vascular ring)
   (c) Evidence of airspace disease consistent with aspiration or cystic fibrosis
   (d) Both a and b
   (e) All of the above

3. Which of the following is *not* a common allergen associated with allergic asthma?

   (a) House dust mite antigen
   (b) Cat and dog danders
   (c) Cockroach antigen
   (d) Tobacco smoke
   (e) Pollens and mold spores

4. Which of the following is a cause of variable extrathoracic airway obstruction?

   (a) Vocal cord polyps
   (b) Paradoxical vocal cord motion
   (c) Tracheomalacia of the intrathoracic airway
   (d) Both a and b
   (e) All of the above

5. Which of the following is a cause of variable intrathoracic airway obstruction?

   (a) Mediastinal adenopathy
   (b) Paradoxical vocal cord motion
   (c) Vocal cord polyps
   (d) Foreign body
   (e) Tracheal stenosis

6. Which of the following is true about hypersensitivity pneumonitis?

   (a) A low CD4 to CD8 ratio is typically found in a bronchoalveolar lavage
   (b) A high CD4 to CD8 ratio is typically found in a bronchoalveolar lavage
   (c) Oral steroids are not typically used from a treatment standpoint
   (d) Antifungal agents are first-line therapy in patients with hypersensitivity pneumonitis
   (e) All of the above are false

7. Which of the following is *not* a clinical feature that should raise suspicion for paradoxical vocal cord motion?

   (a) Minimal or lack of response to aggressive asthma therapy
   (b) Triggers of stress, anxiety, or other emotional factors
   (c) Subjectively more difficulty on inspiration than expiration
   (d) Flattened expiratory flow-volume loop
   (e) Patients with moderate to severe persistent asthma

8. The gold standard for diagnosing paradoxical vocal cord dysfunction is

   (a) Spirometry
   (b) Chest radiograph
   (c) Airway fluoroscopy
   (d) Laryngoscopy
   (e) Ultrasound of vocal cords

9. First-line therapy for the treatment of paradoxical vocal cord motion commonly involves:

   (a) Beta adrenergic agents and inhaled glucocorticoids
   (b) Speech therapy maneuvers
   (c) Nebulized lidocaine
   (d) Biofeedback
   (e) Continuous positive airway pressure

10. Mechanisms for the association of gastroesophageal reflux disease and asthma include:

    (a) Aspiration of gastric contents into the lung with consequent bronchospasm
    (b) Reflux-induced activation of a vagovagal reflex arc from the esophagus to the lung causing bronchoconstriction

(c) A side effect of proton pump inhibitors
(d) Both a and b
(e) All of the above

Answers

1. (e) A positive API score requires recurrent episodes of wheezing during the first 3 years of life and 1 of 2 major criteria (physician-diagnosed eczema or parental asthma) or 2 of 3 minor criteria (physician-diagnosed allergic rhinitis, wheezing without colds, or peripheral eosinophilia ≥ 4%).
2. (e) Chest radiographs may be useful to display findings consistent with asthma, such as hyperinflation, peribronchial thickening, and mucoid impaction with atelectasis, findings suggestive of congenital malformations (e.g., a right aortic arch suggestive of a vascular ring), or evidence of airspace disease consistent with aspiration or cystic fibrosis.
3. (d) Tobacco smoke is *not* a common allergen associated with allergic asthma. It is an irritant.
4. (d) Vocal cord polyps and paradoxical vocal cord motion are causes of variable extrathoracic airway obstruction.
5. (a) Mediastinal adenopathy is a cause of variable intrathoracic airway obstruction.
6. (a) A low CD4 to CD8 ratio is typically found in a bronchoalveolar lavage.
7. (d) A flattened expiratory loop is *not* a clinical feature that should raise suspicion for paradoxical vocal cord motion. One often sees a flattened inspiratory loop.
8. (d) Direct visualization of the vocal cords via laryngoscopy while the patient is having symptoms remains the gold standard for diagnosing paradoxical vocal cord motion.
9. (b) First-line therapy for the treatment of paradoxical vocal cord motion commonly involves speech therapy maneuvers.
10. (d) Mechanisms for the association of gastroesophageal reflux disease and asthma include aspiration of gastric contents into the lung with consequent bronchospasm and reflux-induced activation of a vagovagal reflex arc from the esophagus to the lung causing bronchoconstriction.

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Chapter 10
Chronic Obstructive Pulmonary Diseases Conundrums

Heba Ismail, Andrew Chan, and Samuel Louie

Abstract Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality worldwide. Clinicians and researchers have only recently recognized the disease heterogeneity and systemic consequences from tobacco smoking in aging COPD patients. Diagnosis and management of COPD and its acute exacerbations that begin to occur regularly after FEV_1 has declined to less than 40–60% of predicted is a conundrum encountered frequently in clinical practice. Perhaps the most important challenge is the need to diagnose COPD in earlier stages, beginning in the fifth decade of life, at least a decade before the familiar albeit terminal phenotypes of chronic bronchitis ("blue bloater") and emphysema ("pink puffer") emerge. Persisting poor exercise tolerance despite the use of bronchodilators and inhaled corticosteroids should alert the clinician to the presence of co-morbidities associated with COPD, especially those that resemble acute exacerbation. COPD can often present as conundrums, singularly or severally in a patient. Thus enhancing the knowledge, skills and professional performance of an integrated COPD health care team to provide comprehensive COPD management may improve patient outcomes via early treatment and/or prevention of serious complications secondary to COPD.

Keywords COPD • Obstructive sleep apnea • Pulmonary hypertension • Disproportionate pulmonary hypertension • Pulmonary embolism • Chronic cough • Chronic bronchitis • DLco • Asthma–COPD overlap syndrome

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Case 1

A 75-year-old white female was referred to our pulmonary clinic for evaluation of dyspnea on exertion for several years. According to the patient, her shortness of breath was of gradual onset with a significant decrease in her exercise tolerance over the past 1 year.

Review of systems revealed chronic cough, mainly in the mornings, with production of thick white sputum. She denied any hemoptysis, chest pain, orthopnea, or paroxysmal nocturnal dyspnea. No recent weight changes, fever, chills, or night sweats were endorsed. Past medical history was significant for hyperlipidemia and hypertension.

There was no family history of asthma or other lung diseases. She had stopped smoking 5 years previously, having accumulated a 30 pack-year history. She denied any alcohol or drug abuse. Medications included albuterol metered-dose inhaler to be used as needed for dyspnea. On physical examination, her vital signs revealed a blood pressure of 130/70 mmHg, a heart rate of 75 beats/min, a respiratory rate of 14–16 breaths/min, and SpO_2 on room air of 92%, which decreased to 86% on ambulation. The patient's body mass index (BMI) was 25.

Head and neck examination revealed no pallor or jugular venous distension. Lung auscultation demonstrated diminished breath sounds bilaterally, without wheezing. Cardiovascular examination revealed a regular rhythm, normal first and second heart sounds. Abdominal examination was soft, nontender without palpable organomegaly. The lower extremities had palpably normal pulses bilaterally, without peripheral edema or clubbing. Pertinent laboratory findings included a normal complete blood count, blood urea nitrogen, and creatinine. No pulmonary function test (PFT) was available at the time of her initial presentation to our clinic.

A chest radiograph (Fig. 10.1), displayed hyperinflation of the lungs, without cardiomegaly or acute infiltrates.

With the Presented Data, What Is Your Working Diagnosis?

Although exercise intolerance is the cardinal symptom of untreated COPD, it remains nonspecific since it presents with a myriad of other diseases and disorders. Differential diagnoses at this point include COPD (emphysema or chronic bronchitis), asthma–COPD overlap syndrome, pulmonary infections (subacute–chronic), heart failure, and sleep related disorders versus other etiologies.

COPD from α-1 (alpha-1) antiprotease disease (1–3% of COPD cases, men and women equally affected, more common in Caucasians than in African Americans) is very unlikely given her age, but should be suspected in any adolescent and adult even in their fifth decade of life. Three-quarters of patients with this genetic disorder will develop pulmonary emphysema, which is accelerated when the patient smokes tobacco.

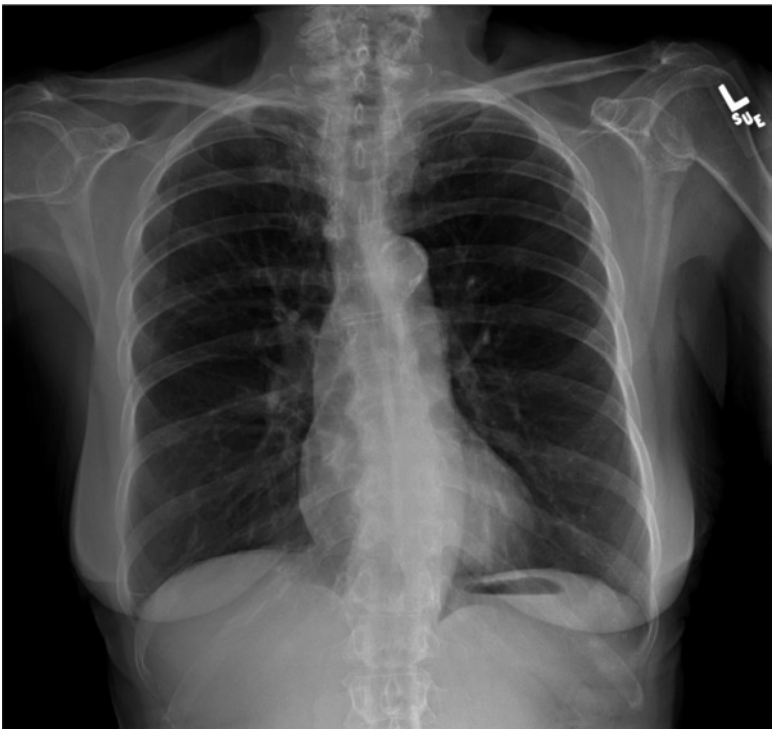

Fig. 10.1 Chest radiograph showing evidence of hyperinflation. No abnormal pulmonary infiltrates identified. The heart and the mediastinum appear unremarkable and the aorta is calcified and tortuous

Recurring episodes of acute bronchitis requiring antibiotic treatment in a patient without an antecedent history of sinusitis or pharyngitis may be a clue to current smoking. Spirometry should be performed once the acute infection is resolved.

Chronic lung infections cannot be entirely ruled out; however, it is unlikely with the current clinical settings and absence of symptoms and signs suggestive of chronic infection, such as low-grade fever, weight loss, fever, chills, or night sweats.

Further evaluation of COPD should include a thorough search for accompanying co-morbidities. Despite the absence of suspicious physical examination findings, cardiovascular disease such as diastolic heart failure needs to be considered in the presence of a complaint of exertional dyspnea.

Sleep-related disorders could be associated with any of the above, which worsen the underlying pulmonary and/or cardiac disease.

Physical deconditioning, depression, and anxiety can accompany each of the above conundrum presentations. Finally, it is important to recognize increasing prevalence of COPD in women, and not to mistake it for asthma when the patient is a smoker. If incorrectly diagnosed and untreated, COPD will cause a progressive decline in exercise tolerance, quality of life, and premature mortality.

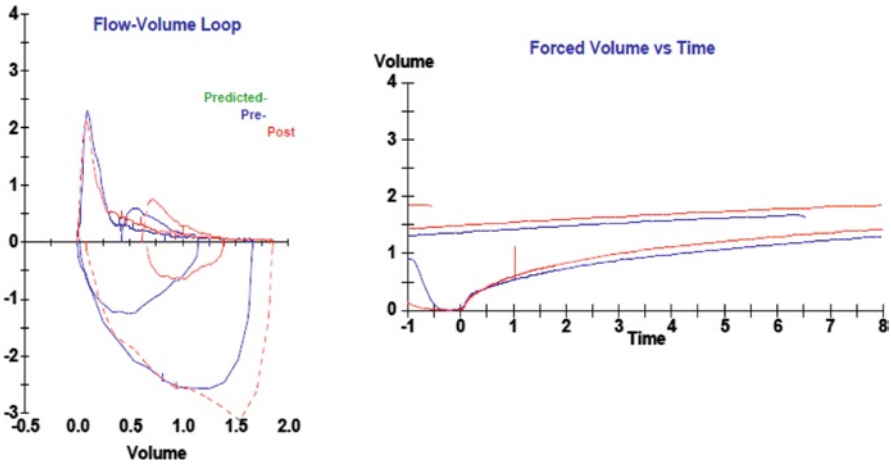

Fig. 10.2 Flow volume loop, pre- and postbronchodilator treatment

What Is the Next Step to Confirm the Diagnosis?

1. PFT, including spirometry, lung volumes, DLco, and flow-volume loops
2. Doppler echocardiography
3. Sputum collection for Gram stain and cultures
4. Sleep study

Spirometry should be performed to confirm the diagnosis of COPD (FEV_1/FVC ratio < 0.70 and FEV_1 less than 80% of predicted value), with the absence of alternative explanations such as severe asthma, vocal cord paralysis, or chronic bronchiectasis. The severity of COPD can be determined by postbronchodilator FEV_1 expressed as a percentage of predicted. For example, postbronchodilator FEV_1 between 50% and 80% of predicted would classify the severity of the patient's COPD as Moderate Stage II in accordance with the GOLD guidelines [1].

The flow-volume loops (Fig. 10.2) and the PFT results (Table 10.1) of the patient are illustrated. Lung volumes may document static hyperinflation with abnormal increases in FRC, RV, and indirectly, RV/TLC and IC/TLC ratios, where FRC represents functional residual capacity, RV residual volume, TLC total lung capacity, and IC inspiratory capacity. An IC/TLC ratio of less than 25% augurs for a very poor survival. A decrease in DLco suggests a reduction in capillary blood volume and can occur in emphysema as well as anemia, interstitial lung disease, and pulmonary vascular disease. Asthma is expected to show a normal DLco, but a normal value does not rule out COPD. Interpretation of DL/VA measurements in COPD are not recommended because of the perils of peripheral air trapping that lead to a falsely low alveolar volume.

Based on the above findings, a diagnosis of COPD was made.

Table 10.1 Pulmonary function test, including spirometry pre and postbronchodilators, lung volumes, and DLco

Spirometry			Pre		Post	
		PRED	Best	%PRED	Best	%PRED
FVC	L	1.94	1.78	92	1.86	96
FEV_1	L	1.46	0.54	37	0.61	42
FEV_1/FVC	%	77	30		33	
Lung volumes						
	Units	PRED	Best		%PRED	
TLC	L	4.14	5.63		136	
RV	L	2.04	3.77		184	
IC/TLC	%		23			
RV/TLC	%	47	67			
Diffusing capacity						
	Units	PRED	Best		%PRED	
DLco	mL/mmHg/min	16.3	6.3		39	
DLVA Adj.	mL/mmHg/min	4.17	2.26		54	

Which COPD Stage Does This Patient Have?

1. Stage I COPD
2. Stage II COPD
3. Stage III COPD
4. Stage IV COPD

Assessment of COPD severity and impact on daily activities of living depends on the patient's level of symptoms, the severity of obstruction based on the spirometric findings, and the presence of complications such as pulmonary hypertension (PH) and/or respiratory failure.

COPD is divided into four stages based on the degree of airflow limitation and obstruction noted on spirometry and assessed using FEV_1% of predicted (Table 10.2). Spirometry and COPD staging document the severity of airways obstruction but do not differentiate between the COPD conundrums. The National Lung Health and Education Program recommends spirometry testing of all smokers 45 years and older or anyone with a chronic cough, sputum production, dyspnea on exertion, or wheezing.

The prognosis and risk of mortality from COPD can be assessed using the BODE score, a relatively simple approach that uses a combination of the abovementioned variables. The BODE method gives a composite score of four components: B represents body mass index (BMI); O represents obstruction (FEV_1 % predicted); D represents dyspnea score (based on the Medical Research Council (MRC) four-point scale, that ranges from "not troubled with breathlessness" to "too breathless to leave the house or breathless while dressing/undressing"); and E represents exercise (6-min walk distance).

This patient was diagnosed with stage III (severe) COPD.

Table 10.2 Stages of COPD based on FEV_1% predicted, with management of each stage. This table is based on the Global Strategy for the diagnosis, management and prevention of COPD, global initiative for chronic obstructive lung disease (GOLD) 2010

COPD stage and characteristics	Management
Mild	
$FEV_1/FVC < 70\%$	• Avoidance of risk factors
$FEV_1 > 80\%$ predicted with or without symptoms	• Vaccination • Short-acting bronchodilators when needed
Moderate	
$FEV_1/FVC < 70\%$	• Avoidance of risk factors
$50\% \leq FEV_1 < 80\%$ with or without symptoms	• Vaccination • Short-acting bronchodilators when needed + • Regular treatment with one or more long-acting bronchodilators • Pulmonary rehabilitation
Severe	
$FEV_1/FVC < 70\%$	• Avoidance of risk factors
$30\% \leq FEV_1 < 50\%$ with or without symptoms	• Vaccination • Short-acting bronchodilators when needed • Regular treatment with one or more long-acting bronchodilators • Pulmonary rehabilitation + • Inhaled glucocorticosteroids if repeated exacerbations
Very severe	
$FEV_1/FVC < 70\%$	• Avoidance of risk factors
$FEV_1 < 30\%$ or $FEV_1 < 50\%$ with chronic respiratory failure	• Vaccination • Short-acting bronchodilators when needed • Regular treatment with one or more long-acting bronchodilators • Pulmonary rehabilitation • Inhaled glucocorticosteroids if repeated exacerbations + • Add long-term oxygen if chronic respiratory failure • Consider surgical treatment

Available from http://www.goldcopd.org

Discussion

The international Global initiative on Chronic Obstructive Lung Disease (GOLD), (WHO/NIH 2010) defines COPD as:

> A preventable and treatable disease with some significant extra pulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases [1].

This definition no longer describes emphysema or chronic bronchitis – terms that remain familiar to the public. COPD is much more a small airways (<2 mm) disease, pathologically a chronic bronchiolitis caused predominantly by prolonged exposure to tobacco smoke. Destructive alveolar wall rupture occurs later, if not concomitantly, from an imbalance between elastases and antielastases, and prolonged activation of neutrophils and macrophages causing regional elastin damage with alveolar emphysema distributed irregularly in a centriacinar pattern. Loss of lung elastic recoil is the key pathophysiological finding which occurs with emphysema perhaps before loss of alveolar wall and capillary surface area measurable by carbon monoxide diffusing capacity (DLco). Collpase of small airways during expiration leads to air trapping and further static hyperinflation. These early changes are not detectable by simple PFT but reliance on the $FEV_1/FVC < 0.70$ and $FEV_1\%$ of predicted remains the current state of the art in COPD screening and staging. A normal DLco does not rule out COPD.

Importantly, no blood test, imaging study, or lung function can completely describe impairment from COPD. The BODE index is a valuable tool for predicting survival in clinical research and assessing disease burden and impairment utilizing BMI, FEV_1 expressed as percentage of predicted, severity of dyspnea (the cardinal symptom of COPD), and exercise capacity or 6-min walk distance (6 MWD) [2].

COPD is marked by greater heterogeneity in clinical phenotypes than bronchial asthma. The reduction in FEV_1/FVC and in FEV_1 percentage of predicted is the common thread linking very different COPD phenotypes and their frequent overlap. Clinical features allow segregation into discrete phenotypes both for clinical care and also further research into disease pathogenesis and may allow reassessment of previous concepts of COPD subsets [3] (Figs. 10.3 and 10.4).

Cluster analysis in COPD has suggested that different phenotypes have different symptoms (dyspnea) and outcomes (exacerbation numbers and mortality) and also differ in age and accompanying comorbidities such as heart disease and osteoporosis [4]. These increasingly reported observations underscore the conundrums of COPD management in practice and may help contribute to personalizing COPD care and treatments based on clinical response.

Ten clinical COPD conundrums (Table 10.3) expand upon the most familiar phenotypes of COPD–chronic bronchitis and/or emphysema and COPD–asthma overlap. We have chosen to address conundrums that can be recognized in practice by poor clinical responses to standard pharmacotherapy or by frequent COPD exacerbations, rather than enter a discourse on a new taxonomy for COPD phenotypes. Several conundrums can occur in the same patient during the course of COPD. Personalizing treatment and management to fit a patient's COPD severity and comorbidities, including pulmonary rehabilitation and palliative care, will become the new standard of care.

The goals of a comprehensive COPD management program are to (1) achieve smoking cessation; (2) control symptoms of dyspnea, cough; (3) reduce and prevent acute exacerbations; and (4) to return patients to their highest level of function to conduct activities of daily living. The pulmonologist must recognize the various stages of COPD with different presenting phenotypes and, in our opinion, different conundrums.

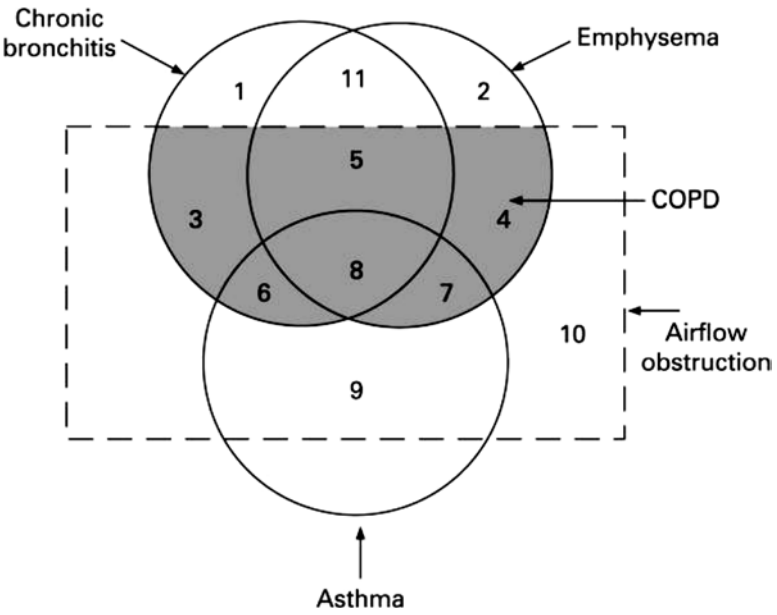

Fig. 10.3 Nonproportional Venn diagram of chronic obstructive pulmonary disease (COPD) produced by the American Thoracic Society. The subsets comprising COPD are shaded. Subset areas are not proportional to the actual relative subset sizes. Asthma is by definition associated with reversible airflow obstruction although, in variant asthma, special maneuvers may be necessary to make the obstruction evident. Patients with asthma whose airflow obstruction is completely reversible (subset 9) are not considered to have COPD. Because in many cases it is virtually impossible to differentiate patients with asthma whose airflow obstruction does not remit completely from persons with chronic bronchitis and emphysema who have partially reversible airflow obstruction with airway hyperreactivity, patients with unremitting asthma are classified as having COPD (subsets 6, 7, and 8). Chronic bronchitis and emphysema with airflow obstruction usually occur together (subset 5), and some patients may have asthma associated with these two disorders (subset 8). Individuals with asthma who have been exposed to chronic irritation, as from cigarette smoke, may develop chronic productive cough, which is a feature of chronic bronchitis (subset 6). Persons with chronic bronchitis and/or emphysema without airflow obstruction (subsets 1, 2, and 11) are not classified as having COPD. Patients with airway obstruction due to diseases with known etiology or specific pathology such as cystic fibrosis or obliterative bronchiolitis (subset 10) are not included in this definition (Reproduced with permission from Marsh et al.) [3]

Management of COPD

The pharmacological treatment of this patient with stage III severe COPD is daily use of long-acting bronchodilators (tiotropium and either salmeterol or formoterol) with an inhaled corticosteroid and a referral to pulmonary rehabilitation. Management of COPD does not begin and end with drug treatment and smoking cessation. COPD is progressive in its clinical course and require integration of health care services, including physician, allied health care specialists, family, and most importantly, the COPD patient who may be accustomed to a strictly sedentary life style. Comprehensive

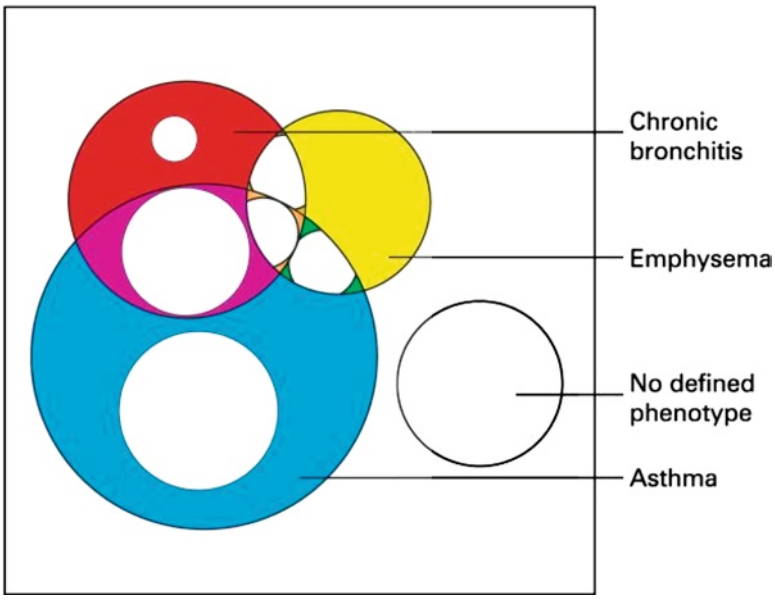

Fig. 10.4 Proportional Venn diagram presenting the different phenotypes within the Wellington Respiratory Survey study population. The large *black rectangle* represents the full study group. The *clear circles* within each *colored area* represent the proportion of subjects with COPD (postbronchodilator forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) < 0.7). The isolated *clear circle* represents subjects with COPD who did not have an additional defined phenotype of asthma, chronic bronchitis, or emphysema (Reproduced with permission from Marsh et al.) [3]

Table 10.3 COPD Conundrums

1.	COPD–Emphysema and/or chronic bronchitis
2.	COPD–Asthma overlap syndrome
3.	COPD–Sleep-related disorders, including obstructive sleep apnea
4.	COPD–Cardiovascular diseases
5.	COPD–Pulmonary hypertension
6.	COPD–Pulmonary embolism
7.	COPD–Lung cancer
8.	COPD–Depression and anxiety
9.	COPD–Alpha-1 antiprotease deficiency
10.	Severe asthma without COPD

COPD management can be divided into two broad categories, pharmacological and nonpharmacological treatment (Table 10.2) that rely on each other to achieve favorable results. There is an overemphasis on pharmacological treatment. None of the existing pharmacological treatment has shown to delay the inexorable course of COPD as measured by the annual rate of FEV_1 decline except smoking cessation and, to an extent, oxygen treatment but pharmacotherapy does offer the COPD patient the opportunity to tolerate and benefit from nonpharmacological interventions by improving lung function and controlling lung hyperinflation.

Oxygen therapy is often used for more advanced and debilitating stages of COPD and, once required, the prognosis is poor with a 2 year mortality of approximately 50%. Instead, as in asthma, the goals of management are to control symptoms and prevent acute exacerbations. There are encouraging signs that this is the correct management strategy, but initiation of effective treatment later in life, that is the seventh decade of life and during more severe stages of COPD, significantly reduces the chance for better outcomes, including survival.

Pulmonary Rehabilitation

According to the American Thoracic Society (ATS) statement on pulmonary rehabilitation, it is defined as a "multidisciplinary program of care for patients with chronic respiratory impairment that is individually tailored and designed to optimize physical and social performance and autonomy." Pulmonary rehabilitation improves quality of life, by improving exercise tolerance and dyspnea. Pulmonary rehabilitation was found to increase peak workload by 18%, and peak oxygen consumption by 11% [5, 6].

Pulmonary rehabilitation should be considered for COPD patients with reduced exercise tolerance and limitation of their daily activities secondary to their disease. Pulmonary rehabilitation program includes exercise training (endurance training and strength training), education, and psychosocial and behavioral intervention in addition to nutritional therapy. In most cases, patients are referred to pulmonary rehabilitation in advanced cases; however, we recommend referral of COPD patients to pulmonary rehabilitation program during earlier stages of the disease to allow for early intervention which may lead to improvement in symptoms and quality of life.

Oxygen Therapy

Long-term oxygen therapy (more than 15 h a day) has been shown to improve survival, exercise tolerance, and pulmonary hemodynamics including pulmonary artery pressure (PAP), lung mechanics, and mental status [7]. Indications of long-term oxygen therapy include PaO_2 at or below 55 mmHg or SaO_2 of less than or equal to 88%; or PaO_2 between 55 and 60 mmHg; or SaO_2 of 89% if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive heart failure, or polycythemia.

Fear of carbon dioxide (CO_2) retention should not dissuade the clinician from prescribing oxygen. A reduction in hypoxic "drive" is one of two explanations for this observation. The respiratory center becomes less sensitive to chronically elevated CO_2 levels, which no longer stimulate respiratory drive. Instead, low PaO_2 provides the primary drive for breathing in these patients. An alternative explanation is that supplemental oxygen causes vasodilation and an increase in perfusion of alveoli previously shunted because of poor ventilation. As a result of changes in ventilation to perfusion ratios, a larger fraction of blood will be directed to poorly ventilated

lung segments, resulting in increase of the CO_2 concentration remaining in the blood and hence CO_2 retention measurable by $PaCO_2$. The clinical consequences today are much less alarming given the pulse oximetry monitoring guidelines for titrating supplemental oxygen.

Clinical Course

The patient was started on inhaled fluticasone/salmeterol, 500/50 twice daily, albuterol MDI as needed, in addition to home oxygen 2 L/min, and was enrolled in the pulmonary rehabilitation program, with significant improvement in her dyspnea and physical activity within 6 months.

Case 2

A 76-year-old white female was referred to us for evaluation of progressive dyspnea on exertion for 1 year. PFT demonstrated: $FEV_1/FVC < 70\%$; FEV_1 of 60% predicted; normal lung volumes and DLco. She was diagnosed with stage II (moderate) COPD, was started on an inhaled long-acting β2 (beta-2) agonist, short acting bronchodilator, and was enrolled in a pulmonary rehabilitation program. However, the patient continued to complain of gradual worsening of her shortness of breath, mainly on walking for more than two miles or climbing a flight of stairs, despite treatment for more than 8 months. She denied any associated chest pain or orthopnea. Review of systems revealed chronic productive cough with white sputum for few years; difficulty sleeping at night; significant snoring (according to her husband); and increased daytime sleepiness. Patient had unintentional weight gain of 40 lb over the past 2 years that was explained by a recent diagnosis of hypothyroidism.

Past medical history was significant for hypothyroidism. There was no family history of lung disease. She stopped smoking 8 years ago, having accumulated 25 pack-year history. Medications included albuterol MDI, salmeterol MDI, and levothyroxine.

On physical examination, her vital signs revealed a blood pressure of 135/80 mmHg, a heart rate of 80 beats/min, a respiratory rate of 14–16 breaths/min, and SpO_2 on room air of 94%, without significant decrease on ambulation. The patient's BMI was 35.

Head and neck examination revealed no pallor or jugular venous distension. Lung auscultation demonstrated diminished breath sounds bilaterally, without wheezing. Cardiovascular examination revealed a regular rhythm, normal first and second heart sounds, and a systolic ejection murmur, grade 2/5, over the aortic area. Abdominal examination was soft, nontender without palpable organomegaly. The lower extremities had palpably normal pulses bilaterally, without peripheral edema or clubbing.

Pertinent laboratory findings included a normal complete blood count, blood urea nitrogen, and creatinine. Her last TSH and free T_4 were normal. Chest radiograph was unremarkable.

With the Presented Data, What Is Your Working Diagnosis?

This case illustrates the difficulties of managing COPD patients who have other comorbidities. Contrast how the task differs from treating acute infectious diseases where clinical and laboratory responses are clearly defined. The clinical course of COPD is affected by clinical phenotype, disease severity, and response to pharmacological and nonpharmacological interventions. But what if the clinical response(s) experienced by the patient with prescribed treatments (pharmacotherapy, smoking cessation, pulmonary rehabilitation) is less than expected? Treatment of COPD will often expose an underlying co-morbidity that continues to cause dyspnea. Differential diagnoses at this point include related comorbidities and conundrums often missed by the primary care providers (Table 10.3). Sleep-related disorders, heart failure, and pulmonary hypertension cannot be ruled out with the currently available history, physical examination, and laboratory findings.

We will discuss each of these comorbidities, including prevalence, clinical presentation, diagnosis, and treatment.

Sleep and COPD

Normal physiological changes in a healthy person during sleep include a decrease in respiratory response to chemical, mechanical, and cortical inputs; a decrease in tidal volume and minute ventilation which leads to an increase in partial pressure of CO_2; and a decrease in the partial pressure of arterial blood oxygen. Sleep-related disorders in COPD patients could be divided into two major groups: the first group includes patients who have sleep-related gas disturbances, and in this group, hypoxemia and hypercapnea are more exaggerated especially during the REM phase of sleep. The associated nocturnal decrease in oxygen saturation could be significant, leading to cardiac arrhythmias and an acute increase in pulmonary artery pressure in the short term, with right-sided heart failure in the long term. These cardiac changes related to COPD are explained by different mechanisms including hypoventilation and/or worsening of ventilation/perfusion mismatch; the second group includes patients who have co-existing sleep apnea and COPD (overlap syndrome). The prevalence of sleep apnea in COPD patients is similar to the normal population of the same age; however, the degree of oxygen desaturation at night is much worse in COPD patients [8].

All COPD patients should be evaluated for sleep-related disorders. An awake arterial blood gas is considered a good indicator of nocturnal oxygen desaturation.

Table 10.4 Indications for right heart catheterization in suspected COPD-pulmonary hypertension

1. ECHO evidence for hemodynamically significant tricuspid regurgitation
2. Marked dyspnea (grade 4 or 5) despite optimization of COPD care
3. Hypocapnea (median $PaCO_2$ 32 mmHg)
4. Very low DLco out of proportion to expectations and spirometry
5. Anticipated treatment of pulmonary hypertension in COPD
6. Exclude left heart failure

Overnight sleep studies like polysomnography are indicated only when there is a suspicion of sleep apnea or when they have other comorbid conditions that are related to severe hypoxemia such as polycythemia and/or cor pulmonale.

Although, there is no evidence that nocturnal oxygen therapy improves survival in patients with COPD and nocturnal hypoxemia, it continues to be prescribed by physicians, with some data suggesting that patients with exacerbations are more likely to die at night especially if they have associated hypercapnea. At median follow-up of 3.4 years, the mortality rate was significantly higher among COPD patients with nocturnal oxyhemoglobin desaturation [9].

In patients with co-existing COPD and sleep apnea, or patients with severe hypoxemia not corrected with oxygen therapy, bilevel positive airway pressure (BIPAP) is recommended, and it is more effective than continuous positive airway pressure (CPAP).

COPD and Pulmonary Hypertension

One of the well-known complications of COPD is pulmonary hypertension (PH). It is defined as a mean pulmonary artery pressure (PAP) of >20 mmHg at rest, which is different from the standard definition of pulmonary arterial hypertension (PAH) defined as a mean PAP > 25 mmHg. However, in some recent studies, PH secondary to COPD was defined using the latter standard.

The exact prevalence of pulmonary hypertension resulting from COPD remains unknown, especially with mild to moderate COPD, since right heart catheterization is not performed on all patients with COPD for ethical reasons. Indications of right heart catheterization (RHC) in COPD patients are summarized in Table 10.4.

A few studies based on hospitalized patients have estimated the prevalence of PH secondary to COPD as defined by a mean PAP > 20 mmHg to range between 35% and 90% [10, 11].

The mechanisms of development of PH in COPD patients include increase in pulmonary vascular resistance secondary to alveolar hypoxia and/or increase in pulmonary capillary wedge pressure (PCWP) during exercise in patients with severe emphysema and hyperinflation. PH in COPD patients can be divided into two main features, the first one occurring at rest in the setting of stable COPD. The majority of these patients will have a mild degree of PH with an average mean PAP of

25–30 mmHg. However, if the mean PAP is >40 mmHg, it is usually associated with cardiopulmonary disease, acute exacerbation, or disproportionate PH which will be discussed separately.

The second feature includes worsening of PH during exercise, sleep, or COPD exacerbation. Worsening of PH with a marked increase in mean PAP is noted in patients with advanced COPD and PH at rest. In these patients, a mean PAP of 25 mmHg during rest may increase to 50–60 mmHg during exercise, sleep, or acute COPD exacerbations, which lead to symptoms of dyspnea on even daily activities like climbing or walking [12, 13].

Disproportionate Pulmonary Hypertension

Many COPD patients develop mild PH with a resting mean PAP of 25–30 mmHg. A minority of patients are, however, noted to have a marked increase of mean PAP to >35–40 mmHg after exclusion of other causes of PH.

A study done by Chaouat et al., comparing patients with COPD with mild versus severe PH showed that patients with COPD and severe PH have less severe airflow obstruction with a mean FEV_1 of 50%; however, they were noted to have profound hypoxemia, hypocapnea, and a severe reduction in DL_{CO} [10].

Two hypotheses have been proposed to explain disproportionate PH in these patients: The first one suggests increased response and reactivity of pulmonary vessels to hypoxia, and the second hypothesis suggests coexisting other forms of pulmonary vascular disease that remain yet unidentified.

No definitive noninvasive diagnostic test exists for pulmonary hypertension in COPD patients. Neither the electrocardiogram nor the chest radiograph is sensitive or specific. The DLco is often severely reduced out of proportion to other pulmonary function metrics but its decrease is not specific for pulmonary hypertension. Doppler echocardiography (ECHO) is often inaccurate in these patients secondary to body habitus, and the chance of obtaining tricuspid regurgitation signals of sufficient quality is generally low. Furthermore, resting ECHO fails to document significant increases in pulmonary pressures during exercise in COPD patients, which may mislead clinicians in the accurate diagnosis of this disease.

Right heart catheterization (RHC) remains the gold standard for diagnosis of PH in these patients. Direct measurements of the PAP, pulmonary capillary wedge pressure (PCWP), right heart filling pressures, and cardiac output can be obtained. RHC can be performed at rest, during steady-state exercise, and after therapeutic interventions (vasodilators).

There are no clear guidelines regarding indications of treatment of PH in COPD patients. The necessity of treatment of mild or moderate PH in these patients remains questionable; however, some may argue that acute increase in PAP with worsening of PH during acute COPD exacerbations and/or exercise may contribute to development of right-sided heart failure.

Prior to initiation of treatment, all patients must have RHC to evaluate PH severity and to rule out other explanations for dyspnea such as left-sided heart failure. Treatment may include oxygen therapy and pulmonary vasodilators. Long-term oxygen therapy should be prescribed as clinically indicated since it has been shown to reverse and/or stabilize PH over a period of 2–6 years [14, 15]. However, the subphenotypes of responders are not yet clearly defined.

PAH-specific medical therapy including epoprostenol, prostacyclin analogues, phosphodiesterase-5 inhibitors, and endothelin receptor antagonists were tested in randomized controlled trials, leading to approval of several drugs. However, a recent study included COPD patients with mild resting PH or no PH treated with bosentan or placebo showed no improvement in pulmonary hemodynamics but a worsening of gas exchange abnormalities, primarily hypoxemia [16].

What Is the Next Diagnostic Test Needed in This Patient?

1. Doppler echocardiography
2. Right heart catheterization
3. Polysomnography

Polysomnography confirmed the diagnosis of obstructive sleep apnea. She was started on BIPAP, with inspiratory positive pressure of 10 cm H_2O and expiratory positive pressure of 5 cm H_2O during sleep, which significantly improved her sleep quality.

Clinical Course

The patient continued to complain of shortness of breath on minimal exertion during the daytime. Doppler echocardiography showed good images with an elevated estimated right ventricular pressure of 60 mmHg and normal left ventricular function. She underwent right and left cardiac catheterization, which revealed a right ventricular pressure of 48 mmHg with an end-diastolic pressure of 6 mmHg, a pulmonary artery pressure of 46/14 mmHg with a mean of 29 mmHg, and pulmonary capillary wedge pressure of 9 mmHg. Further workup for other causes of pulmonary hypertension was negative and the patient was diagnosed with PH secondary to COPD. The patient was started on a phosphodiesterase-5 inhibitor sildenafil and experienced significant improvement in her symptoms, including shortness of breath and exercise tolerance. Her functional capacity remained stable for a few months; however, in early autumn the same year, she experienced an acute episode of severe shortness of breath whereby she was unable to ambulate except for a few steps, and experienced no relief from increasing her home oxygen flow rate to 4 L/min. The patient was brought in emergently to the Emergency Department at UC Davis Medical Center.

Table 10.5 Definition of acute COPD exacerbation

1.	An acute change in dyspnea, cough, and/or sputum sufficient enough to warrant therapy change (ATS-ERS, 2004)
2.	An event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD (GOLD, 2009)

The patient denied any cough, fever, or chills. She denied any recent history of upper or lower respiratory tract infection. She complained of mild chest pain that was pleuritic in nature but did not endorse dizziness or syncope. She was in respiratory distress with accessory muscle use. Vital signs showed a blood pressure of 90/60 mmHg, a heart rate of 110–120 beats/min with a regular rate, a temperature of 98° F, a respiratory rate of 25 breaths/min, and an SpO_2 of 85% on face mask with an FiO_2 of 0.7. Breath sounds were diminished bilaterally with minimal expiratory wheeze. Cardiovascular examination was unchanged without an increase in P2 or new heart murmurs.

Pertinent laboratory findings include a normal complete blood count. Arterial blood gas on FiO_2 of 0.7 showed: pH of 7.35, $PaCO_2$ of 45 mmHg (baseline $PaCO_2$ of 60), and PaO_2 of 55 mmHg (baseline PaO_2 of 65). Biomarkers for cardiac injury, including troponins and creatine kinase, were checked on three separate occasions 6–8 h apart and results were within normal range. Electrocardiogram showed sinus tachycardia. Chest radiology showed no evidence of pulmonary infiltrates or pneumothorax.

The patient received albuterol and ipratropium nebulizer treatment, in addition to one dose of intravenous methylprednisolone without significant improvement for the following 18 h.

Discussion

The clinical picture is consistent with an acute exacerbation of COPD, defined as an acute change in a patient's baseline dyspnea, cough, and/or sputum beyond day-to-day variability, sufficient to warrant a change in therapy.

Exacerbations are common causes of morbidity and mortality in COPD patients (Table 10.5). Depending on severity, patient may only require treatment at home, acute hospitalization for monitoring, or the intensive care unit for frank acute respiratory failure requiring noninvasive ventilation or mechanical ventilation. Despite appropriate treatment, approximately 33% of COPD patients with acute COPD exacerbations who were discharged from the Emergency Department will have recurrent symptoms in 2 weeks' time, and nearly 20% will relapse and require further hospital care.

Table 10.6 Risk factors and causes for acute COPD exacerbation

Risk factors
1. Advancing age
2. Continued tobacco smoking or nicotine addiction
3. Failure to take long-acting bronchodilators if prescribed
4. Failure to take inhaled corticosteroids if prescribed
5. Failure to take long-term oxygen therapy if prescribed
6. Failure to take influenza vaccine and pneumococcal vaccine
7. Lack of regular exercise or failure to participate in pulmonary rehabilitation
8. Depression and anxiety
Causes in addition to COPD progression with aging
1. Infections – most common cause, especially viral or bacterial (50–60%), and can range from acute bronchitis to severe pneumonia with sepsis
2. Environmental air pollution (5–10%)
3. Left heart failure and/or coronary artery disease (5–20%)
4. Unknown (30%), but consider acute pulmonary embolism in 25%
5. Pulmonary arterial hypertension (1–5%)
6. Cardiac arrhythmias
7. Overlapping asthma exacerbation

The causes of COPD exacerbations can be both infectious and noninfectious (Table 10.6). Different COPD phenotypes may be more prone to develop exacerbations. Until COPD biomarkers are discovered for early diagnosis and to help monitor management, the primary care clinicians and consultants should consider and maintain a large differential diagnosis when presented with a patient who fails to improve after smoking cessation despite correct use of long-acting anticholinergics, β-2 (beta-2) agonist bronchodilators and inhaled corticosteroid treatments – an example of one of ten COPD conundrums (Table 10.3).

COPD and Pulmonary Embolism

Pulmonary embolism should be considered in all patients presenting with acute COPD exacerbations, especially if no clear etiology is identified. A study done by Sidney et al., showed that COPD patients have approximately twice the risk of developing pulmonary embolism and other venous thromboembolic events [17]. The exact prevalence of PE in COPD patients remains unclear. A systematic review and meta-analysis done by Rizkallah et al., showed one of four COPD patients who require hospitalization for an acute exacerbation may have PE [18]. A prospective cohort study done by Tillie-Leblond showed that the incidence of pulmonary embolism was 25% in a series of consecutive patients with COPD referred for severe exacerbation of unknown origin.

Using the Geneva score, three risk factors were statistically associated with pulmonary embolism: history of venous thromboembolism, malignant disease, and decrease in $PaCO_2$ at least by 5 mmHg. The clinical presentation and physical examination of acute PE in COPD patients remain nonspecific. Seventy-three percent of patients have dyspnea and tachypnea, 30% have tachycardia, and 66% have pleuritic chest pain at the time of presentation. More specific physical findings in acute PE may include hemoptysis, elevated neck veins, loud P2 component of the second heart sound, and asymmetry in the size of lower extremities or calf tenderness.

The classic features of PE on chest X-rays (CXR), including Westermark's sign or Hampton's Hump, have poor sensitivity in the setting of COPD. Arterial blood gas findings are nonspecific; however, hypoxemia and hypocapnea (especially in the setting of prior hypercapnea with known COPD) have been found to be associated with pulmonary embolism in COPD patients. The presence of mildly elevated brain natriuretic peptide (BNP) and troponins in the setting of COPD exacerbation may indicate an embolic event. Further studies with EKG, serial troponins, and echocardiogram should follow to rule out ischemia and differentiate between right and left ventricular dysfunction. D-Dimer is considered the preferred diagnostic tool in the outpatient and emergency department settings, as it has a similar distribution in patients with and without COPD, and in conjunction with pretest probability, a negative D-Dimer and low pretest probability exclude thromboembolic disease. Since COPD patients develop DVT at a rate similar to patients in the intensive care unit, lower extremity Doppler ultrasounds may be used as an early test to help detect thromboembolic events. Spiral computed tomography (CT) of the chest is the "gold" standard test for diagnosis of PE. When the patients have a contraindication to intravenous contrast, V/Q scan can be considered; however, its utility has been declining secondary to frequent nondiagnostic results of indeterminate probability.

Clinical Course

The patient underwent bilateral lower extremity venous Doppler ultrasonography, which was positive for bilateral deep vein thrombosis, followed by spiral CT of the chest that showed evidence of acute pulmonary embolism. The patient was started on a heparin infusion with significant improvement in her symptoms. She was subsequently discharged home on oral warfarin.

The exact duration of treatment of venous thromboembolic events in COPD patients remains undefined. According to the American College of Chest Physicians' (ACCP) guidelines, patients with a first episode of unprovoked venous thromboembolic event with PE, and in whom risk factors for bleeding are absent and for whom good anticoagulation monitoring is achievable, long-term treatment with vitamin K antagonist (VKA) is recommended (grade 1A). The patient was prescribed warfarin lifelong, based on the assumption of satisfactory monitoring of her INR. She continues to be clinically stable with infrequent COPD exacerbations.

Questions

1. A 66-year-old man presents to his physician's office with a 6 month history of wheezing, dyspnea on exertion, and chronic productive cough, mainly in the mornings with white sputum production. He has 40 pack-year smoking history. Physical examination reveals diminished breath sounds bilaterally with mild end-expiratory wheezes. Pulmonary function tests show an FEV_1 of 1.5 L/sec (60% predicted), an FVC of 2.3 L, with an FEV_1/FVC of 0.65, normal lung volumes and DLco. He is currently on long-acting bronchodilators, with short-acting bronchodilators as needed.

   Which of the following interventions will be most effective for improving the patient's long-term survival?

   (a) Inhaled anticholinergics
   (b) Inhaled corticosteroids
   (c) Long-term oral corticosteroids
   (d) Smoking cessation

2. A 65-year-old male with COPD has an FEV_1 of 28% predicted. In addition to the spirometry data, the recently described BODE score provides useful survival prediction data in this type of patient.

   What additional data are required to calculate the BODE score?

   (a) PaO_2, $PaCO_2$, and 6-min walk test (6MWD)
   (b) Arterial pH, dyspnea score, and 6 MWD
   (c) Dyspnea score, body mass index (BMI), and 6 MWD
   (d) Arterial pH, BMI, and residual volume

3. A 60-year-old woman has a diagnosis of COPD, with an FEV_1 of 1.1 L/sec (45% predicted) without significant bronchodilator response. Her current regimen includes salmeterol two puffs twice per day, and albuterol two puffs every 6 h as needed. The patient was recently admitted with an acute COPD exacerbation and was treated with antibiotics and a tapering dose of prednisone. Her oxygen saturation on room air is 93%.

   Which of the following is the best management option for this patient?

   (a) Home oxygen
   (b) Add an inhaled corticosteroid
   (c) Maintain the patient on chronic oral steroid therapy
   (d) Long-term antibiotic treatment

4. A 65-year-old man with a previous diagnosis of COPD. Recent pulmonary function tests showed an FEV_1 of 0.72 L/sec (21% predicted), FVC of 2.88 L (60% predicted), and FEV_1/FVC of 25%. He is currently on long-acting inhaled bronchodilators and inhaled corticosteroids; in addition he uses an albuterol nebulizer every 4 h and prior to bedtime. Despite maximum treatment, he continues to complain of dyspnea on exertion. His wife mentioned that he snores at night

and naps every afternoon. On physical examination, his body mass index (BMI) is 35 kg/m^2 he has diminished breath sounds bilaterally on lung auscultation and his heart and abdominal examination were normal. A resting arterial blood gas on room air showed a pH of 7.41, $PaCO_2$ of 46 mmHg, and PaO_2 of 56 mmHg. The patient was found to have polycythemia on his complete blood count. Chest radiography was normal, without evidence of cardiomegaly or dilated pulmonary arteries, and an echocardiogram showed mild pulmonary hypertension.

What is your next diagnostic step?

(a) Overnight pulse oximetry
(b) Complete polysomnography
(c) CT of the chest
(d) Ventilation/perfusion scan

5. A 70-year-old woman with a history of COPD and hypothyroidism was referred to our clinic for evaluation of progressive dyspnea. She had smoked approximately one pack of cigarettes daily for 35 years and developed exertional dyspnea for 3 years. At that time, she was diagnosed with moderate COPD. The patient was started on inhaled bronchodilators, and stopped smoking. The patient continued to complain of progressive dyspnea. Inhaled bronchodilators had little effect. Three months earlier, she had been admitted to the hospital with a COPD exacerbation. During that admission, she was started on supplemental oxygen therapy. On evaluation, she was comfortable at rest but reported difficulty walking more than 50 ft. She was able to ambulate in the house and perform basic housework but avoided stairs. She denied cough, sputum, wheezing, or chest pain, but did notice some lower extremity edema. A chest radiograph showed large dilated pulmonary arteries bilaterally, cardiomegaly, but no active pulmonary disease. A computed tomographic pulmonary angiogram (CTPA) showed mild emphysematous changes, but no filling defects. PFT's showed: FEV_1 1.27 L/sec (64% predicted); FVC 2.12 L (84% predicted); FEV_1/FVC 0.60, TLC 3.87 L (90% predicted); RV 1.72 L (97% predicted); and DL_{CO} 8.24 (42% predicted), with no significant changes when compared to PFT's performed 6 months prior. A ventilation/perfusion lung scan showed low probability for pulmonary embolism. A transthoracic echocardiogram (TTE) showed normal left ventricular size and systolic function, with a left ventricular ejection fraction of 60–65%. The right ventricular and right atrial dimensions were normal. The right ventricular systolic pressure was estimated at 25 mmHg and the right atrial pressure was assumed to be 5 mmHg.

What is the most likely cause of this patient's dyspnea?

(a) COPD
(b) Right to left intracardiac shunt
(c) Left ventricular systolic dysfunction
(d) Pulmonary hypertension
(e) Chronic thromboembolic disease

Answers and Explanation

1. (d) Smoking cessation.
   Smoking cessation is the single most clinically effective and cost-effective intervention for slowing COPD progression. Inhaled bronchodilators and corticosteroids may reduce the hospitalization rates in COPD patients but have no effect on the rate of decline of FEV_1 or long-term survival in stable COPD patients. Oral corticosteroids can cause severe adverse effects, and do not benefit most of COPD patients.
2. (c) Dyspnea score, body mass index (BMI), and 6 minute walking distance (6 MWD).
   Factors that correlate with survival in COPD patients include: degree of airway obstruction as measured by FEV_1, poor oxygenation, and impaired right cardiac function. More recently, simpler assessments that can be done in many settings have been incorporated into BODE score and have been shown to have strong correlation with survival. The BODE score has four components: B represents BMI; O represents obstruction (FEV_1); D represents dyspnea; and E represents exercise. BODE score of 0–2 has 20–30% 4-year mortality, while BODE score of >7 has 80–90% 4-year mortality.
3. (b) Add an inhaled corticosteroid.
   Regular treatment with inhaled corticosteroids has been shown to reduce the frequency of exacerbations in COPD patients with an $FEV_1 < 50\%$ predicted (stage III and IV COPD) and repeated exacerbations. Long-term treatment with oral corticosteroids is not recommended for COPD patients. The lack of convincing data to support benefits from oral steroids and the presence of significant side effects associated with its use argue against its beneficial role in management of COPD patients. Long-term oxygen therapy is generally indicated in patients with severe COPD, with PaO_2 of <55 mmHg, or SaO_2 at or below 88%, or PaO_2 between 55 and 60 mmHg if there is evidence of pulmonary hypertension, polycythemia, or heart failure.
4. (b) Complete polysomnography.
   The patient has severe COPD based on the PFT results, he continues to complain of dyspnea despite treatment, and has symptoms and signs suggestive of obstructive sleep apnea with evidence of polycythemia on his test results which is a complication of prolonged hypoxemia. This suggests the diagnosis of obstructive sleep apnea (OSA). Overlap syndrome (COPD with OSA) is not uncommon in COPD patients, since it is estimated that <15% of patients with COPD have concomitant OSA. Hypoxemia is exaggerated with patients who have overlap syndrome in comparison to patients who have COPD alone. Overnight sleep studies such as polysomnography are indicated only when there is suspicion of sleep apnea, or when they have other comorbid conditions that are related to severe hypoxemia such as polycythemia and/or cor pulmonale. The patient's symptoms are less suggestive of chronic thromboembolic disease; he has no clear risk factors such as malignancy, or recent surgery with immobilization. A CT of the chest would be helpful to diagnose any underlying lung disease, for

example, interstitial lung disease (ILD); however, this is unlikely since he has no restrictive pattern on his PFT's and no evidence of ILD on his chest radiograph.

5. (d) Pulmonary hypertension.
   Pulmonary hypertension is not uncommon in patients with COPD. Although TTE is a useful screening tool for pulmonary vascular disease, its sensitivity and specificity for diagnosing PH in COPD is more limited secondary to body habitus. This patient had evidence of dilated pulmonary arteries on CXR and CT of the chest, which highly suggests pulmonary hypertension. Chronic thromboembolic pulmonary hypertension can cause progressive dyspnea and enlargement of one or both pulmonary arteries; however, the low probability of the V/Q scan and lack of any filling defects in the proximal arteries on CTPA make this diagnosis unlikely. COPD is a common cause of dyspnea in adult patients with a history of chronic tobacco use. This patient's symptoms, however, appear to be out of proportion to the severity of her lung disease. The progression of her symptoms despite stable (PFT's), tobacco cessation and initiation of bronchodilator therapy argue against COPD as the sole cause of her progressive dyspnea. Although the presence of pulmonary artery dilation with absence of evidence of PH on TTE may raise the suspicion of intracardiac shunt diagnosis, the patient's clinical picture, advanced age, and normal cardiac chambers size argue against significant intracardiac shunt or left ventricular systolic dysfunction.

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Part V
Pulmonary Vascular Diseases

Chapter 11
Pulmonary Hypertension

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Abstract Pulmonary arterial hypertension (PAH) can be idiopathic or associated with other disease processes. Systemic sclerosis is an example of one disease that is associated with the development of PAH. Regardless of the cause, PAH can have an insidious onset and is often difficult to diagnose because of the subtle associated signs and symptoms as well as the lack of a definitive noninvasive diagnostic test.

Keywords Pulmonary hypertension • Systemic sclerosis

Case 1 Shortness of Breath on Exertion

The patient is a 47-year-old woman who presents with shortness of breath. She claims to be an active woman who used to play volleyball and softball until she began to notice progressive dyspnea while playing 1 year ago. Her symptoms have progressed to the point that she is symptomatic while climbing a flight of stairs. At the time of the initial visit, her symptoms were so severe that she was breathless with activities of daily living, including taking a shower and doing the laundry. She denies any symptoms of cough, fevers, chills, and syncope, but she did complain of mild, dull, midsternal chest pain. She also reports occasional palpitations.

There is no history of venous thromboembolism, diet medication use, risk factors for HIV, and use of any illegal drugs other than marijuana as a teenager. The patient

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had a 30-year history of smoking about a half a pack of cigarettes daily; however, she had successfully quit recently. She does, however, complain of occasional muscle aches and joint pains but has not noted any other symptoms suggestive of collagen vascular disease. In terms of her sleep history, she admits to loud snoring and apneas have been witnessed by her spouse.

Her past medical history includes hyperthyroidism, goiter, and a monoclonal gammopathy of unknown significance. Her family's medical history was unremarkable.

Physical Exam

The patient is well developed, well nourished, and in no acute distress. Vitals: weight: 154.9 lb, height: 64 in., pulse: 87 beats/min, SaO_2: 96%, BP: 160/100 mmHg. HEENT: There is no scleral icterus, pupils are equally round and reactive to light and accommodation, and extraocular movements are intact. The nasal passages are narrow but patent. The oropharynx reveals a moderate-sized tongue and a slightly low-lying palate. There is no retrognathia. The neck is supple without lymphadenopathy. Skin: There were no rashes or nodules. CV: The heart had a regular rate and rhythm with a normal S1 but a fixed, split S2. There were no cardiac murmurs, rubs, or gallops. Pulmonary: Lungs are normal to auscultation and percussion. There are no wheezes, rhonchi, or rales. Abdomen: The abdomen is soft and nontender without evidence of hepatosplenomegaly. Extremities: There is no clubbing, cyanosis, or edema. Neurologic: The cranial nerves are intact. Muscle strength is normal, and her gait is normal.

Data

See Tables 11.1 and 11.2.

Imaging Studies

Chest X-ray: Clear lung fields without acute infiltrates or effusions, but with evidence of enlarged pulmonary arteries.

Ventilation/perfusion (V/Q) scan: There are no segmental or subsegmental perfusion defects. There is a normal ventilatory washout. The study is not consistent with pulmonary embolus.

Echocardiogram: Normal left ventricular size with an ejection fraction of 60–65%. There is a flattened ventricular septum, consistent with right ventricular pressure and volume overload. There is left ventricular diastolic dysfunction. The right ventricle is dilated and diffusely hypokinetic with moderate to severe right ventricular systolic dysfunction. There is mild right ventricular hypertrophy. The estimated pulmonary arterial systolic pressure is 90–95 mmHg. The right atrium is dilated. The mitral and aortic valves appear normal.

Table 11.1 Initial blood work

WBC (×10E3/uL) Normal (4.0–10.5)	Hemoglobin (g/dL) Normal (11.5–15.0)	Hematocrit (%) Normal (34.0–44.0)	Platelets (×10E3/uL) Normal (130–400)	TSH (uIU/mL) Normal (0.45–4.5)	ESR Normal (0–10)	HCG beta (mIU/mL)
7.0	15.2 (H)	45.4 (H)	217	4.6	6	<1

(H): higher than normal value

Table 11.2 Initial blood work (continued)

Albumin (g/dL) Normal (3.5–5.5)	Total bilirubin (mg/dL) Normal (0.1–1.2)	Direct bilirubin (g/dL) Normal (0–0.4)	Alkaline phosphatase (IU/L) Normal (25–150)	AST (IU/L) Normal (0–40)	ALT (IU/L) Normal (0–40)	LDH (IU/L) Normal (100–190)
4.4	0.6	0.15	55	96 (H)	93 (H)	331 (H)

(H): higher than normal value

With the Presented Data, What Is Your Working Diagnosis?

This previously healthy 47-year-old woman presented with slowly progressive dyspnea in the absence of any history of or risk factors for cardiopulmonary disease. The physical exam reveals signs of right-sided heart failure and the suggestion of polycythemia. Echocardiographic findings further contribute to the diagnosis of pulmonary hypertension (PH) in the absence of significant left-sided heart dysfunction. The working diagnosis is severe PH.

Differential Diagnosis

The differential diagnosis includes idiopathic pulmonary arterial hypertension (IPAH) versus PH associated with connective tissue disease. Less likely is PH associated with chronic thromboembolic disease, chronic undiagnosed pulmonary parenchymal disease, and sleep-disordered breathing.

Workup

Right heart catheterization is performed.
See Tables 11.3 and 11.4.

Pulmonary function testing: see Tables 11.5–11.7.

6-min-walk test (6 MWT): The distance walked in 6 min is 413 m. The resting oxygen saturation on room air is 97%. The oxygen saturation drops to 90% with exertion. The patient does not require oxygen during testing.

Table 11.3 Right heart catheterization hemodynamic pressures

Pulmonary artery (S/D/M), mmHg	Pulmonary capillary wedge, mmHg	Right atrium mean, mmHg	Right ventricle (S/D), mmHg
90/25/52	8	8	90/16

Table 11.4 Right heart catheterzation cardiac output and calculations

		Hemodynamic resistance
Cardiac output by Fick, L/min	Cardiac index by Fick, L/min/m^2	Pulmonary vascular resistance (Woods Units)
2.29	1.26	20.55

Table 11.5 Pulmonary function test-spirometry

	Ref	Pre measured	Pre % predicted	Post measured	Post % predicted	Post % change
FVC (L)	3.25	3.71	114	3.73	115	1
FEV_1 (L/s)	2.70	2.81	104	2.83	105	1
FEV_1/FVC (%)	84	76		76		
$FEF_{25–75\%}$ (L/s)	3.03	2.31	76	2.31	76	0

Ref reference, *Pre* pre-bronchodilator, *Post* post-bronchodilator

Table 11.6 Pulmonary function test-lung volumes

	Reference	Pre measured	Pre % reference
VC (L)	3.25	3.71	114
TLC (L)	5.00	5.81	116
RV (L)	1.73	2.10	122
RV/TLC (%)	34	36	

Pre pre-bronchodilator

Table 11.7 Pulmonary function test-carbon monoxide diffusion capacity

	Reference	Pre measured	Pre % reference
DLCO mL/mmHg/min	23.1	21.7	94

Pre pre-bronchodilator

ANA: negative, RF: negative, ANCA: negative, HIV: negative, TSH: normal, ESR: 6 (normal 0–10), BNP 80 (normal 0–100).

See Table 11.8 for the ANCA panel results.

Baseline polysomnogram reveals mild obstructive sleep apnea with an apnea-hypopnea index (AHI) of 8.5 events/h. There is a component of REM-related sleep disordered breathing, as her REM (AHI) is significantly elevated at 37.2 events/h. The lowest oxygen saturation during the night was 83%. Mild snoring was present during the night.

Table 11.8 ANCA panel

MPO Ab (U/mL) Normal (<9)	PR-3 Ab (U/mL) Normal (<3.5)	C-ANCA (titer) Normal (<1:20)	P-ANCA (titer) Normal (<1:20)	Atypical P-ANCA (titer) Normal (<1:20)
<9	<3.5	<1:20	<1:20	<1:20

Follow-up echocardiography revealed decreased pulmonary artery pressure followed by increased right ventricular size.

What Is Your Diagnosis and Why?

Severe IPAH. All serologic testing is negative. Polysomnography reveals only mild OSA, V/Q lung scanning does not reveal signs of chronic thromboembolic disease, PFTs are not consistent with intrinsic lung disease.

The patient is initially treated with a phosphodiesterase 5 (PDE 5) inhibitor, sildenafil and because of a low cardiac output, a selective endothelin receptor antagonist was added. Functionally the patient was initially classified NYHA III but she improved to NYHA II with the ability to climb stairs without dyspnea. She then further improved to NYHA I and was able to play softball twice a week and volleyball once a week. The patient was additionally anticoagulated with warfarin.

Case 2 Woman with Scleroderma and Dyspnea

This patient is a 46-year-old woman with a history of scleroderma with associated Raynaud's phenomena and gastroesophageal reflux that was diagnosed 25 years prior to presentation. She initially presented to a pulmonologist's office because of a change in her exercise tolerance. Prior to presentation, she had been able to run 3 miles at a time without difficulty, however, at the time of presentation she was unable to run 100 yards without dyspnea. In addition, she describes difficulty in breathing during activities of daily living such as vacuuming. She denies significant coughing and lower extremity edema. She is a life-long nonsmoker and denies any history of illicit drug use. She has no other significant past medical history.

Physical Exam

In general, the patient is not in acute distress. Vital Signs: BP: 112/80 mmHg, HR: 73 beats/min, RR:16 breaths/min, Weight 125 lb, SaO_2: 100% HEENT: The sclera are anicteric and there are no cervical or supraclavicular adenopathy, thyromegaly,

Table 11.9 Initial blood work

WBC (×10E3/uL) Normal (4.0–10.5)	Hemoglobin (g/dL) Normal (11.5–15.0)	Hematocrit (%) Normal (34.0–44.0)	Platelets (×10E3/uL) Normal (130–400)	TSH (uIU/mL) Normal (0.45–4.5)
5.9	12.4	36.2	267	3.55

Table 11.10 Initial blood work (continued)

Albumin (g/dL) Normal (3.5–5.5)	Total bilirubin (mg/dL) Normal (0.1–1.2)	Direct bilirubin (g/dL) Normal (0–0.4)	Alkaline phosphatase (IU/L) Normal (25–150)	AST (IU/L) Normal (0–40)	ALT (IU/L) Normal (100–190)
3.6	0.3	0.07	97	32	22

Table 11.11 Pulmonary function test-spirometry

Spirometry						
	Ref	Pre measured	Pre % reference	Post measured	Post % reference	Post % change
FVC (L)	3.00	2.51	84	2.44	81	–3
FEV_1 (L)	2.52	1.97	78	2.01	80	2
FEV_1/FVC (%)	84	90		92		
$FEF_{25–75\%}$ (L/s)	2.88	1.85	64	2.60	90	41

Ref reference value, *Pre* pre-bronchodilator, *Post* post-bronchodilator

or oropharyngeal lesions or exudates. There is increased jugular venous distention with a positive hepatojugular reflux to the angle of her jaw. CV: S1 is normal, there is an increased S2P2. There is no RV heave. There are no murmurs, rubs, or gallops. Lung sounds are clear bilaterally. Abdomen is soft and nontender with adequate bowel sounds, without hepatosplenomegaly. Extremities reveal typical discoloration of her digits due to Raynaud's phenomenon with well-healed ulcerations at her fingertips. Sclerodactaly is obvious. Otherwise, there is no clubbing, cyanosis, or edema. Skin exam reveals tightness around her mouth, nose, and ankles. There are no telangiectasias. Neurologic deficits are not found.

Data

See Tables 11.9–11.13.

A 6-min walk test revealed a room air arterial oxygen saturation of 100%. She walked 445 m and desaturated to as low as 96%. She did not require supplemental oxygen but she did become tachycardic with a heart rate of 130 bpm.

Table 11.12 Pulmonary function test-lung volumes

	Reference	Post measured	Post % reference
VC (L)	3.00	2.44	81
TLC (L)	4.60	4.16	90
RV (L)	1.55	1.72	111
RV/TLC (%)	34	41	

Post post-bronchodilator

Table 11.13 Pulmonary function test-carbon monoxide diffusion capacity

	Reference	Post measured	Post % reference
DLCO mL/mmHg/min	19.1	12.8	67

Imaging Studies

CT scan of the thorax: 6 mm nodule in the right middle lobe and 6 mm nodule in the left lower lobe. There are no significant mediastinal nodes. There are no other masses or infiltrates found.

Echocardiogram: LVEF 70%, RV estimated to be normal in size and function with peak pulmonary systolic pressures between 35 and 40 mmHg. Mild tricuspid regurgitation is noted.

With the Presented Data, What Is Your Working Diagnosis?

Limited-type scleroderma possibly with associated pulmonary hypertension and likely without interstitial lung disease.

Diagnosis

The diagnosis of limited-type scleroderma is well established for this patient. Lung disease associated with systemic sclerosis (SSc) is common and can occur in the form of interstitial lung disease (ILD) and/or PAH. Given the patient's symptoms, either one of these complications is a possibility. Interestingly, the physical exam finding of an increased S2P2 is the only sign of PH. Otherwise, the echocardiogram did not reveal signs of PH and the PFTs and chest CT scan did not reveal signs of ILD.

Table 11.14 Right heart catheterization-pressures

Pulmonary artery (S/D/M), mmHg	Pulmonary capillary wedge, mmHg	Right atrium mean, mmHg	Right ventricle (S/D), mmHg
20/5/12	3	1	20/5

Table 11.15 Right heart catheterization-cardiac output and pulmonary vascular resistance

		Hemodynamic resistance
Cardiac output by Fick L/min	Cardiac Index by Fick L/min/m^2	Pulmonary vascular resistance (Woods Units)
4.34	2.78	2.07

Workup

A repeat CT scan of the chest reveals stable, sub-centimeter parenchymal nodules. There continues to be no evidence of alveolitis or interstitial disease.

Right heart catheterization: See Tables 11.14 and 11.15.

Follow-up echocardiogram reveals an LV ejection fraction of 60%. RV wall thickness was increased and its systolic pressure is mildly increased. The estimated right ventricular systolic pressure is 41 mmHg. There is associated mild tricuspid regurgitation.

Baseline polysomnogram revealed moderate obstructive sleep apnea syndrome with an AHI 18.6 events/h.

Follow-up echocardiogram 3 years later reveals an LV ejection fraction of 55%. The RV systolic pressure was mildly to moderately increased with an estimated systolic pressure of 45 mmHg and mild tricuspid regurgitation was noted.

Follow-up CT scan: A repeat CT scan of the chest again reveals stable, sub-centimeter parenchymal nodules. There continues to be no evidence of alveolitis or interstitial disease; however, there now appears to be enlargement of the main pulmonary arteries (Fig. 11.1).

Follow-up right heart catheterization: See Tables 11.16 and 11.17.

What Is Your Diagnosis and Why? Limited-type scleroderma with associated pulmonary hypertension.

Follow-Up

The patient was started on a PDE 5 inhibitor, which was successful in treating the digital ulcers due to Raynaud's phenomenon. Interestingly, she continues to have no to minimal evidence of PH on echocardiogram for 3 years after her presentation. She was also started on an endothelin receptor antagonist based on echocardiographic progression.

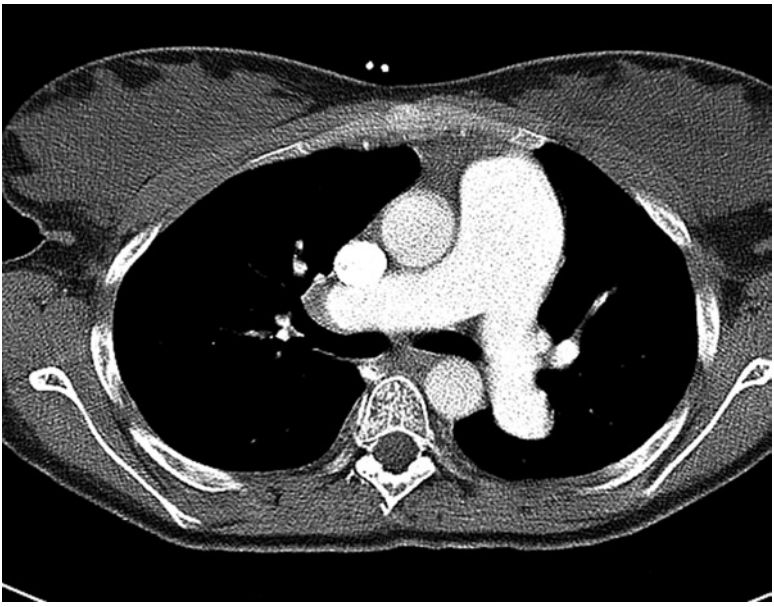

Fig. 11.1 Chest CT scan demonstrating a large main pulmonary artery, which has a larger diameter than the aorta

Table 11.16 Right heart catheterization-pressures

Pulmonary artery (S/D/M), mmHg	Pulmonary capillary wedge, mmHg	Right atrium mean, mmHg	Right ventricle (S/D), mmHg
60/17/36	5	3	60/11

Table 11.17 Right heart catheterization-cardiac output and pulmonary vascular resistance

		Hemodynamic resistance
Cardiac output by Fick L/min	Cardiac index by Fick L/min/m^2	Pulmonary vascular resistance (Woods Units)
3.83	2.45	8.10

Discussion

Pulmonary arterial hypertension (PAH), whether idiopathic or associated with a connective tissue disease, carries a poor prognosis. Furthermore, a New York Heart Association (NYHA) functional class of III or IV, the presence of Raynaud's phenomenon, an elevated mean right atrial pressure, an elevated mean pulmonary artery pressure, a decreased cardiac index, and reduced diffusing capacity for carbon monoxide (DLCO) are also associated with a reduced survival. The estimated median survival time is 2.8 years for untreated idiopathic PAH [1].

Classification of Pulmonary Hypertension

Pulmonary hypertension (PH) was previously classified as either primary or secondary pulmonary hypertension. Primary or unexplained pulmonary hypertension is now called idiopathic pulmonary arterial hypertension (IPAH). However, because there are some forms of secondary pulmonary hypertension that resemble IPAH in both histopathology as well as response to treatment, a new classification scheme has been developed [2]. There are five groups of pulmonary hypertension. Group 1 consists of sporadic IPAH, heritable IPAH, and PAH caused by diseases that affect small pulmonary muscular arterioles. Diseases included in this category include connective tissue diseases, HIV infection, portal hypertension, congenital heart disease, schistosomiasis, chronic hemolytic anemia, persistent pulmonary hypertension of the newborn, pulmonary veno-occlusive disease, and pulmonary capillary hemagiomatosis. Also included in this category is PAH caused by drugs and toxins. Appetite suppressant use increases the risk of developing PAH as does the chronic use of cocaine or amphetamines.

Group 2 consists of PH caused by left heart disease whether it results from systolic, diastolic, or valvular dysfunction. Group 3 includes PH resulting from lung disease or alveolar hypoxia. Group 4 is a category consisting of PH due to chronic thromboembolic disease. Group 5 is a miscellaneous category that includes diseases such as sarcoidosis and other causes. The cases presented fall into the group 1 category and it is these diseases that have been studied extensively from the PH therapeutics standpoint.

Brief History and Prevalence

Pulmonary arterial hypertension was first described by Ernst von Romberg in 1891 as "sclerosis of the pulmonary arteries." Since the first World Symposium on Pulmonary Hypertension in 1971, PH was defined as a mean pulmonary artery pressure (PAPm) ≥25 mmHg at rest or >30 mmHg with exercise in the presence of a normal pulmonary capillary wedge pressure (≤15 mmHg). However, the definition was revised at the 4th World Symposium on Pulmonary Hypertension in 2008 in Dana Point, California. The exercise criterion was removed from the definition of PH due to the wide variation in pulmonary artery pressures during exercise in normal, healthy individuals as well as the increases that occur with aging. Patients who have mean pulmonary artery pressures above 20 mmHg but <25 mmHg may be described as having borderline PH.

The prevalence of group 1 PH patients with idiopathic PAH is estimated to be 15 cases per 1 million adults. The prevalence of PAH associated with SSc varies depending on the method of diagnosis and the definition used. Those with limited SSc (formerly referred to as the CREST syndrome) with calcinosis cutis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasias have an incidence of 8–12% [3]. The incidence of PAH associated with other connective tissue diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) is less than that of SSc.

Presentation (Signs and Symptoms)

The most common presenting symptoms of PAH are dyspnea and fatigue. As the disease progresses, chest pain, lightheadedness/syncope, and edema become more common as right-sided heart failure develops and progresses. Less common symptoms include cough, hemoptysis, and hoarseness.

The physical exam may reveal a loud pulmonic component to the second heart sound (S2P2) on cardiac exam. Additionally, the S2P2 may be palpable at Erbs point (left parasternal second or third intercostal space). As the right ventricle fails, the second heart sound becomes split and a sternal heave can be seen and felt. Other signs of right heart strain include increased jugular venous pressure, hepatojugular reflux, a right-sided S3 or S4, a holosystolic tricuspid regurgitant murmur, ascites, and edema. The likelihood that PAH is present is increased when signs of right heart failure are found on physical examination [4].

Pathophysiology

PAH is a proliferative vasculopathy that is characterized by endothelial cell proliferation, intimal fibrosis, vasoconstriction, and perivascular fibrosis. Pathology reveals intimal hyperplasia and fibrosis, medial smooth muscle hypertrophy, and scattered in situ thrombus in the small pulmonary arteries and arterioles. It is thought that the development of PAH begins with an underlying genetic predisposition, followed by a second hit or stimulus that activates the disease process. IPAH is usually sporadic, though 6–10% may have a hereditary influence. Up to 25% of sporadic cases of IPAH have abnormal bone morphogenetic protein receptor type II (BMPR2) found in the blood, which may also play a role in familial PAH. Other genetic abnormalities include mutations in activin-like kinase type 1 and 5-hydroxytryptamine transporter (5HTT) genes.

Systemic sclerosis (SSc) is a heterogeneous disorder that is characterized by dysfunction of the endothelium and dysregulation of fibroblasts that results in excessive production of collagen and abnormalities of the immune system [5]. Progressive fibrosis of the skin and internal organs results in organ failure and ultimately death. Pulmonary manifestations of SSc include PAH, interstitial fibrosis, and increased risk of pulmonary malignancies. The pulmonary vascular lesions in PAH associated with SSc are indistinguishable from those found in IPAH.

Workup: Laboratory Studies and Diagnostic Procedures

Although an electrocardiogram (EKG) is an inadequate screening tool for PAH, some classic findings may aid in developing a diagnostic suspicion. EKG findings for PAH include right axis deviation and RV hypertrophy. Findings of RA enlargement such as p-pulmonale and RV hypertrophy found on an EKG predict decreased survival.

Chest radiography should be performed as part of the initial workup of PAH, but similar to EKG, findings are nonspecific. Findings of PAH on CXR include enlarged main pulmonary arteries and hilar shadows, peripheral "pruning" of vessels, and loss of the retrosternal airspace on lateral CXR which suggests RV enlargement.

Pulmonary function testing (PFTs) often reveals mild ventilatory restriction and a moderately decreased diffusion capacity for carbon monoxide in up to 50% of IPAH patients [6]. Additionally, PFTs are important to perform in order to identify any underlying lung disease that may be contributing to the PH. Subjects with scleroderma are routinely screened for the development of PAH because of the increased mortality associated with it. A decreased or decreasing DLCO or an increased FVC/DLCO ratio can predict the development or progression of PAH [7].

Echocardiography is considered to be the noninvasive screening test of choice to screen for the presence of PH. Echocardiography requires accurate measurement of the tricuspid regurgitant jet for an estimation of pulmonary artery systolic pressure. Signs of right-sided heart failure may be seen on echocardiogram with RV pressure overload, paradoxical bulging of the ventricular septum, and RV and RA hypertrophy. Additionally, information about left-sided heart function can be gathered to provide information regarding the cause of PH. However, the estimation of pulmonary artery pressures may either overestimate or underestimate pulmonary artery pressures in as many as 48% of patients [8]. Because of the possible inaccuracies in measuring pulmonary pressures that can occur with echocardiography, right heart catheterization is considered the "gold standard" for the diagnosis of pulmonary hypertension.

All patients with group 1 PH (except those with portopulmonary hypertension) should undergo vasoreactivity testing. A positive response is defined by a decrease in the mean PAP of at least 10 mmHg to a value of ≤40 mmHg along with an increased or unchanged cardiac output and a minimally reduced or unchanged systemic blood pressure. Pulmonary arterial vasoreactivity can be determined during a right heart catheterization using intravenous adenosine or prostacycline or inhaled nitric oxide.

PAH may be idiopathic or associated with various connective tissue diseases including systemic sclerosis (SSc), systemic lupus erythematosis (SLE), rheumatoid arthritis (RA), and mixed CTD (MCTD). Anti-fibrillarin antibodies (anti-U3-RNP) are frequent in SSc-PAH patients. Antinuclear antibody (ANA), rheumatoid factor (RF), and antineutrophil cytoplasmic antibody (ANCA) testing should be performed to rule out connective tissue disease associated with pulmonary hypertension. Additionally, chronic hemolytic anemia and schistosomiasis should be excluded as contributing factors in the correct clinical setting. HIV status should be checked along with liver function testing to rule out portopulmonary hypertension.

Management/Treatment

Early identification and initiation of treatment is recommended for patients that have PH. Primary therapy is directed at the underlying cause driving the PH. Group 1 PH therapy will be discussed separately. The therapy for group 2 PH is aimed at

the treatment of the underlying heart disease, while therapy for group 3 PH is directed toward treating the underlying lung disease and reversing alveolar hypoxia. Reversing nocturnal hypoxemia with oxygen or continuous positive airway pressure should be pursued if there is nocturnal hypoventilation or obstructive sleep apnea. PH due to chronic thromboembolic disease (group 4) should be treated with anticoagulant therapy. Selected patients benefit from surgical thromboendarterectomy. Therapy for group 5 PH is directed at the underlying disease process causing the PH.

There are several therapies that should be considered for PH regardless of the cause. The cautious use of diuretics is recommended to treat fluid overload. Oxygen therapy likely benefits all groups of PH, though long-term data only exist for group 3. Anticoagulation is indicated in IPAH, hereditary PAH, drug-induced PAH, and group 4 PH. Patients with PH are at increased risk for pulmonary thromboembolism due to slow pulmonary blood flow, venous stasis, dilated right ventricle, and a sedentary lifestyle [9]. Additionally exercise training leads to increased 6-min walk distance, improvements in WHO functional class, and maximally achieved oxygen consumption with exercise [10]. However, exercise does not improve hemodynamic abnormalities.

Both cases presented above are examples of group 1 PH. These patients have pulmonary arterial hypertension and have been studied extensively with a variety of therapeutics. Therapy for group 1 patients who are WHO functional class II–IV should be initiated. Those who have a positive vasoreactivity test as mentioned above can be given a trial of oral calcium channel blocker (CCB) therapy. CCB therapy in some patients with positive vasoreactivity leads to prolonged survival along with functional and hemodynamic improvements. Those who do not have a positive vasoreactivity test should be treated with either a prostanoid, an endothelin receptor antagonist, a phosphodiesterase 5 (PDE 5) inhibitor, or occasionally with combined therapy. For appropriate patients who continue to have disease progression despite maximal medical therapy, atrial septostomy or lung transplantation may be considered.

Prostanoid therapies for PAH include intravenous (IV) epoprostenol (Flolan); intravenous, subcutaneous, and inhaled treprostinil (Remodulin); and inhaled iloprost (Ventavis). Therapy with continuous IV epoprostenol has been shown to improve several hemodynamic parameters as well as functional capacity in those with group 1 PH [11]. In those with IPAH, there is an additional survival benefit. Treprostinil improves hemodynamics, symptoms, exercise capacity and may improve survival in group 1 PH.

Endothelin receptor antagonists have been shown to improve exercise capacity, dyspnea and hemodynamics. Bosentan (Tracleer) is an oral, nonselective endothelin receptor antagonist given twice a day. The selective type A endothelin-1 receptor antagonists ambrisentan (Letairis) and sitaxentan (Thelin) also improve exercise tolerance, functional class, hemodynamics, and quality of life in group 1 PH. Dose-related hepatotoxicity is the main side effect that limits administration of bosentan and sitaxentan. Peripheral edema and teratogenicity are also important potential adversities.

The PDE 5 inhibitors, sildenafil (Viagra, Revatio), tadalafil (Cialis, Adcirca), and vardenafil (Levitra) are also oral agents that work by inhibiting cyclic GMP to prolong the effects of endothelial nitric oxide.

The selection of agents should be individualized to each patient's WHO functional class, as well as lifestyle. The use of these medications should be under the guidance of an experienced clinician backed by a center that has a strong interest in PH. Care should be taken to consider the routes of administration as well as the potential side effects. Women who take endothelin receptor antagonists should be on effective birth control and undergo routine pregnancy testing.

Atrial septostomy, or the surgical creation of a right-to-left shunt, can increase systemic blood flow in those with severe PH and a history of syncope or severe right-sided heart failure despite maximal medical therapy. However, the likelihood of death or clinical worsening in those with a mean right atrial pressure of >20 mmHg, low cardiac output, and resting hypoxemia is significant. Finally, double lung or heart–lung transplantation may be the final treatment option for those with severe, resistant PH.

Questions

1. Which of the following are associated with decreased survival in pulmonary hypertension?

   (a) New York Heart Association (NYHA) functional class of III or IV
   (b) Raynaud's phenomenon
   (c) Elevated mean right atrial pressure, elevated mean pulmonary artery pressure, and decreased cardiac index
   (d) Reduced diffusing capacity for carbon monoxide (DLCO)
   (e) All of the above

2. Pulmonary arterial hypertension is defined as:

   (a) Sclerosis of the pulmonary arteries
   (b) A mean pulmonary artery pressure (PAPm) ≥ 25 mmHg at rest or >30 mmHg with exercise in the presence of a normal pulmonary capillary wedge pressure (≤15 mmHg)
   (c) A mean pulmonary artery pressure (PAPm) ≥ 25 mmHg at rest or >30 mmHg with exercise in the presence of an elevated pulmonary capillary wedge pressure (>15 mmHg)
   (d) A mean pulmonary artery pressure (PAPm) ≥ 25 mmHg at rest in the presence of a normal pulmonary capillary wedge pressure (≤15 mmHg)

3. Which of the following genetic mutation(s) are associated with pulmonary hypertension?

   (a) Activin-like kinase type 1
   (b) Bone morphogenetic protein receptor type II (BMPR2)
   (c) PHOX2b

(d) 5-hydroxytriptamine (serotonin) transporter (5HTT) genes
(e) A, B, and D

4. The gold standard for the diagnosis of pulmonary hypertension is:

(a) Echocardiography
(b) Physical exam
(c) Right heart catheterization
(d) Pulmonary angiogram

5. A positive response to vasoreactivity test is defined as:

(a) An increase in the mean PAP along with an increase in the cardiac output
(b) A decrease in the mean PAP, a decrease in cardiac output, and a decrease in systemic blood pressure
(c) A decrease in the mean PAP of at least 15 mmHg, a decreased cardiac output, and an increase in systemic blood pressure
(d) A decrease in the mean PAP of at least 10 mmHg to a value of ≤40 mmHg, an increased or unchanged cardiac output, and a minimally reduced or unchanged systemic blood pressure

6. Subjects who demonstrate a positive response to vasoreactivity testing:

(a) Should be given a trial of oral calcium channel blocker (CCB) therapy
(b) Demonstrate improved outcomes when treated with sildenafil
(c) Have a worse overall prognosis
(d) More commonly have pulmonary hypertension associated with connective tissue disease

7. Pulmonary hypertension associated with systemic sclerosis (SSc) is considered:

(a) Group 1 PH
(b) Group 2 PH
(c) Group 3 PH
(d) Group 4 PH
(e) Group 5 PH

8. The following therapy(ies) should be considered in all patients with pulmonary hypertension regardless of the cause:

(a) Oxygen
(b) Diuretics
(c) Anticoagulation
(d) Exercise
(e) All of the above

9. Effective therapy for group 1 PAH can be delivered:

(a) Intravenously
(b) Orally

(c) Subcutaneously
(d) Inhalation
(e) All of the above

10. Patients should be referred for lung transplantation:

(a) As soon as the diagnosis of PAH is made
(b) Never
(c) Two years after the diagnosis is made
(d) If there is disease progression despite medical therapy

Answers

1. (e) All of the above. Each of the choices listed above are associated with decreased survival in pulmonary hypertension [1]. Without treatment, the estimated median survival time is 2.8 years for untreated idiopathic PAH.
2. (e) Pulmonary arterial hypertension was first described by Ernst von Romberg in 1891 as "sclerosis of the pulmonary arteries." Since the first World Symposium on Pulmonary Hypertension in 1971, PH was defined as a mean pulmonary artery pressure (PAPm) ≥ 25 mmHg at rest or >30 mmHg with exercise in the presence of a normal pulmonary capillary wedge pressure (≤15 mmHg). However, the definition was revised at the 4th World Symposium on Pulmonary Hypertension in 2008 in Dana Point, California. The exercise criterion was removed from the definition of PH due to the wide variation in pulmonary artery pressures during exercise in normal, healthy individuals as well as the increases that occur with aging. Patients who have mean pulmonary artery pressures above 20 mmHg but <25 mmHg may be described as having borderline PH.
3. (e) Mutations in the activin-like kinase type 1, BMPR2, and 5HTT genes have all been linked to the development of pulmonary hypertension. Mutations in the activin-like kinase type 1 receptor have been demonstrated in some patients with PAH. Abnormal BMPR2 has been demonstrated in up to 25% of patients with IPAH. 5HTT activity has been linked to pulmonary artery smooth muscle hypertrophy. Increased activity has been demonstrated in some patients with IPAH. The PHOX 2b gene is associated with congenital central hypoventilation syndrome.
4. (c) Right heart catheterization is the "gold standard" for the diagnosis of PH. PH is defined as a mean pulmonary artery pressure (PAPm) ≥ 25 mmHg at rest in the presence of a normal pulmonary capillary wedge pressure (≤15 mmHg). Echocardiography is considered to be a screening test for pulmonary hypertension. However, echocardiogram can either overestimate or underestimate pulmonary artery pressures in as many as 48% of patients [8]. Physical exam findings are helpful in the evaluation of patients with PH; however, the physical exam cannot be used to diagnose PH. Pulmonary angiography is not used to diagnose PH.
5. (d) A positive vasoreactivity test is defined by a decrease in the mean PAP of at least 10 mmHg to a value of ≤40 mmHg, an increased or unchanged cardiac output, and a minimally reduced or unchanged systemic blood pressure.

6. (a) CCB therapy in some patients with positive vasoreactivity leads to prolonged survival along with functional and hemodynamic improvements.
7. (a) Pulmonary hypertension associated with SSc is classified as Group 1 PH. SSc pulmonary hypertension is a form of secondary pulmonary hypertension that resembles IPAH in both histopathology as well as response to treatment. There are five groups of pulmonary hypertension. Group 1 consists of sporadic IPAH, heritable IPAH, and PAH caused by diseases that affect small pulmonary muscular arterioles. Diseases included in this category include connective tissue diseases, HIV infection, portal hypertension, congenital heart disease, schistosomiasis, chronic hemolytic anemia, persistent pulmonary hypertension of the newborn, pulmonary veno-occlusive disease, and pulmonary capillary hemangiomatosis. Also included in this category is PAH caused by drugs and toxins. Appetite suppressant use increases the risk of developing PAH as does the chronic use of cocaine or amphetamines. Group 2 consists of PH caused by left heart disease whether it results from systolic, diastolic, or valvular dysfunction. Group 3 includes PH resulting from lung disease or alveolar hypoxia. Group 4 is a category consisting of PH due to chronic thromboembolic disease. Group 5 is a miscellaneous category that includes diseases such as sarcoidosis and other causes. The cases presented fall into the group 1 category and it is these diseases that have been studied extensively from the PH therapeutics standpoint.
8. (e) The cautious use of diuretics is recommended to treat fluid overload. Oxygen therapy likely benefits all groups of PH, though long-term data only exist for group 3. Anticoagulation is indicated in IPAH, hereditary PAH, drug-induced PAH, and group 4 PH. Patients with PH are at increased risk for pulmonary thromboembolism due to slow pulmonary blood flow, venous stasis, dilated right ventricle, and a sedentary lifestyle [9]. Exercise training leads to increased 6-min walk distance, improvements in WHO functional class, and maximally achieved oxygen consumption with exercise [10]. However, exercise does not improve hemodynamic abnormalities.
9. (e) Prostanoid therapies for PAH include intravenous (IV) epoprostenol (Flolan); intravenous, subcutaneous, and inhaled treprostinil (Remodulin); and inhaled iloprost (Ventavis). Oral endothelin receptor antagonists such as Bosentan (Tracleer), ambrisentan (Letairis), and sitaxentan (Thelin) and PDE 5 inhibitors, sildenafil (Viagra, Revatio), tadalafil (Cialis, Adcirca), and vardenafil (Levitra) are also available. The selection of agents should be individualized to each patient's WHO functional class, as well as lifestyle. The use of these medications should be under the guidance of an experienced clinician backed by a center that has a strong interest in pulmonary hypertension. Care should be taken to consider the routes of administration as well as the potential side effects. Women who take endothelin receptor antagonists should be on effective birth control and undergo routine pregnancy testing.
10. (d) Although there are some patients who experience disease progression despite medical therapy and require double lung or heart–lung transplantation, there are now several treatment options for PAH. Prostanoid therapies for PAH include intravenous (IV) epoprostenol (Flolan); intravenous, subcutaneous, and inhaled treprostinil (Remodulin); and inhaled iloprost (Ventavis). Therapy with continuous

IV epoprostenol has been shown to improve several hemodynamic parameters as well as functional capacity in those with group 1 PH [11]. In those with IPAH, there is an additional survival benefit. Treprostinil improves hemodynamics, symptoms, exercise capacity and may improve survival in group 1 PH. Endothelin receptor antagonists have been shown to improve exercise capacity, dyspnea, and hemodynamics. The selective type A endothelin-1 receptor antagonists, ambrisentan (Letairis) and sitaxentan (Thelin) have been shown to improve exercise tolerance, functional class, hemodynamics, and quality of life in group 1 PH. The PDE 5 inhibitors, sildenafil (Viagra, Revatio), tadalafil (Cialis, Adcirca), and vardenafil (Levitra) are also oral agents that work by inhibiting cyclic GMP to prolong the effects of endothelial nitric oxide. Double lung or heart–lung transplantation may be the final treatment option for those with severe, resistant pulmonary hypertension despite medical therapy.

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Chapter 12
Pulmonary Embolism

Amita P. Vasoya and Thomas F. Morley

Abstract Acute pulmonary embolism is known as the great masquerader. Many of the clinical signs and symptoms are nonspecific and may be suggestive of various diseases. However, appropriate and timely diagnosis and treatment are imperative. The goals are to improve survivalship and prevent the long-term sequelae of thromboembolic disease.

Keywords Pulmonary embolism • Deep vein thrombophlebitis • Virchow triad • Indwelling central venous catheters • Cor pulmonale • Dyspnea • Chest pain • Syncope • Anticoagulants

Case 1

A 46-year-old male presented to the emergency room (ER) following a syncopal event at home. His wife heard a "thud" in the bathroom and found the patient face down on the floor. He was unresponsive for about a minute and awakened with amnesia for the event. No seizure activity was witnessed. No cardiac arrhythmia was reported by the EMT personnel who responded to the call. On arrival to the ER, the patient was alert but required 100% FIO_2 to maintain his oxygen saturation. The patient reported experiencing exertional dyspnea for 7 days prior to presentation. In addition, he experienced acute, left-sided, pleuritic chest pain and severe exertional dyspnea 24 h prior to presentation. He denied hemoptysis.

His past medical history was significant for hypertension, asthma, and left deep vein thrombophlebitis 7 years prior to admission following a motor vehicle accident.

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Past surgical history included right knee arthroscopic surgery 10 years prior to admission. Social history was negative for smoking, alcohol usage, or illicit drug use. The patient worked as a corrections officer. Family history was significant in that the patient's brother had a history of pulmonary embolism and deep vein thrombophlebitis. His mother died from gastric carcinoma. Asthma, diabetes mellitus, and hypertension were among other family members.

The patient's medications prior to admission included olmesartan, betamethasone inhaler, diltiazem, fexofenadine, montelukast, and albuterol nebulizer. He had no known drug allergies.

His physical examination was as follows. Vital signs showed temperature 98.6°F, blood pressure 160/70 mmHg, heart rate 75/min, respiratory rate 20/min, and pulse oximeter saturation 98% on FIO_2 of 100% by mask. He was awake, alert, oriented, and in no respiratory distress. HEENT examination was unremarkable except for swelling and laceration of his lower lip. No neck vein distention, masses, or thyromegaly noted. Heart rate and rhythm were normal without murmur, rub, or gallop. The lungs were clear to auscultation. The abdomen was soft, non-tender, and without organomegaly or masses. Stool was heme negative. The extremities were without edema, cyanosis, or clubbing. No thigh or calf tenderness was noted. Neurologic examination was unremarkable.

Further evaluation provided the following information. EKG showed normal sinus rhythm at 70 bpm with small Q-waves in leads III and AVL. Chest x-ray showed borderline cardiomegaly with clear lung fields. Arterial blood gas revealed pH 7.39 (7.35–7.45), $PaCO_2$ 44 mmHg (35–45 mmHg), PaO_2 184 mmHg (80–95 mmHg), HCO_3^- 26 mEq/L (22–26 mEq/L), and saturation of 100% (95–100%) on 100% FiO_2. Serum electrolytes, CBC, and coagulation studies were within normal limits. Serum CPK was negative with a mildly elevated troponin.

With the Presented Data What Is Your Working Diagnosis?

The working diagnosis at this time is extensive. The differential diagnosis includes acute pulmonary embolism, acute myocardial infarction, valvular heart disease, cardiac arrhythmia, pericardial tamponade, bleeding or volume depletion, right ventricular infarction, right to left intracardiac shunt, neurocardiac syncope, or neurologic disorder such as transient ischemic attack or seizure.

Workup

Venous ultrasound Doppler of the lower extremities was negative for deep vein thrombophlebitis.

CT pulmonary angiogram identified multiple, bilateral, proximal filling defects.

2D echocardiogram demonstrated normal left ventricular function with a dilated, hypokinetic right ventricle. A bubble study was negative for intracardiac shunt.

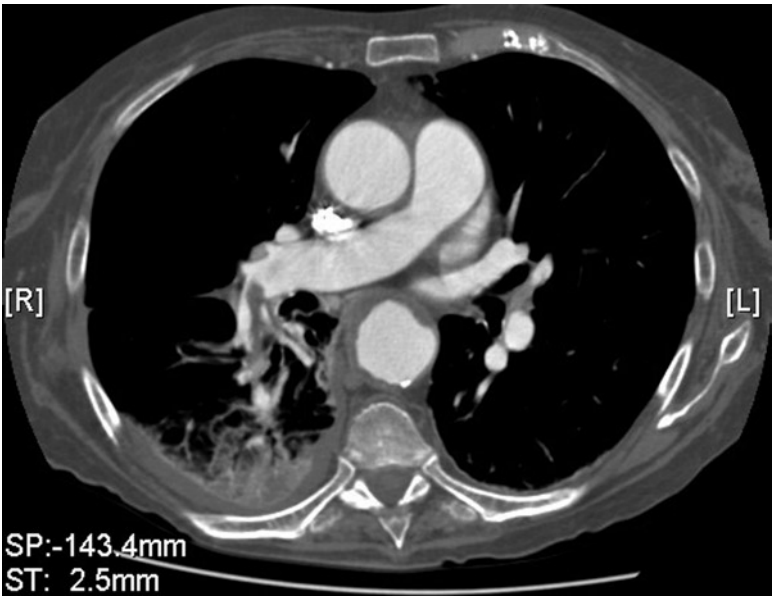

Fig. 12.1 CT pulmonary angiogram at the level of the pulmonary artery show multiple, intraluminal filling defects in the proximal right pulmonary artery consistent with pulmonary emboli. An area of peripheral consolidation is present in the right lower lobe posteriorly consistent with pulmonary infarction

What Is Your Diagnosis and Why?

Syncope is generally due to transient global reduction in cerebral blood flow that results in loss of consciousness and often a fall. There are a large variety of potential causes including neurocardiac syncope, neurologic disorders (e.g., seizure, transient ischemic attack), valvular heart disease (e.g., aortic stenosis), intracardiac shunt, cardiac overload (e.g., hypertensive emergency, pulmonary embolism), or arrhythmias. However, most cases of syncope are not associated with severe hypoxemia and a clear chest radiograph. Massive pulmonary embolism and a right to left shunt could account for these findings. In this case, bedside echocardiogram demonstrated normal left ventricular function with a dilated, hypokinetic right ventricle. A bubble study did not reveal any right to left shunt. CT pulmonary angiogram demonstrated multiple, bilateral, proximal pulmonary emboli (Fig. 12.1). The patient was treated with intravenous lytic therapy (tissue plasminogen activator) and an inferior vena caval filter was placed. A hypercoagulable workup was performed due to the patient's age, history of prior deep vein thrombophlebitis, and family history of venous thromboembolic disease. The patient was positive for protein S deficiency and was maintained on lifelong anticoagulation.

Case 2

A 67-year-old female with a history of metastatic breast cancer to bone presented with acute dyspnea at rest that started on the morning of admission. She denied chest pain, dizziness, fever, cough, hemoptysis, pleurisy, diaphoresis, paroxysmal nocturnal dyspnea, or orthopnea. She complained of bilateral lower extremity edema and feeling "shaky." The EMS responders, upon arrival, noted atrial fibrillation on her heart monitor with a blood pressure was 80/45 mmHg.

Her past medical history was significant for breast cancer with spinal metastasis and emphysema. Past surgical history was positive for breast biopsy. Social history was negative for alcohol or illicit drug use, but positive for 50-pack-year cigarette smoking. Family history was negative.

Her medications included venlafaxine, oxycodone, albuterol inhaler, dexamethasone, fentanyl patch, gabapentin, and alprazolam. She had no known drug allergies.

Her physical examination was as follows. Vital signs showed temperature 98.5°F, blood pressure 112/83 mmHg, heart rate 95/min (regular), respiratory rate 20/min, and pulse oximeter saturation 90% on 4 LPM nasal cannula. The patient was awake, alert, oriented, and in mild respiratory distress. HEENT examination was unremarkable. No neck vein distention, mass, or bruit was noted. Heart rate and rhythm were normal without murmur, rub, or gallop. Lungs demonstrated diminished breath sounds, otherwise clear. The abdomen was soft and non-tender with normal bowel sounds. No organomegaly was noted. Bilateral pedal edema was noted without calf or thigh tenderness. Neurologic examination was negative.

Further evaluation provided the following information. EKG showed sinus tachycardia with premature atrial contractions. Chest x-ray showed cardiomegaly with clear lung fields. Arterial blood gas revealed pH of 7.40 (7.35–7.45), $PaCO_2$ of 41 mmHg (35–45 mmHg), PaO_2 of 70 mmHg (80–95 mmHg), HCO_3^- of 25 mEq/L (22–26 mEq/L), and saturation 95% (95–100%) on 4 LPM oxygen. Serum electrolytes showed Na^+ 139 mEq/L (136–144 mEq/L), K^+ 2.6 mEq/L (3.7–5.2 mEq/L), Cl^- 105 mEq/L (101–111 mEq/L), HCO_3^- 25 mEq/L (20–29 mEq/L), BUN 32 mg/dL (7–20 mg/dL), and creatinine 0.97 mg/dL (0.8–1.4 mg/dL). CBC and coagulation profile were within normal limits.

With the Presented Data What Is Your Working Diagnosis?

Same as outlined for Case 1.

Workup

Venous ultrasound Doppler of the lower extremities showed left ileofemoral deep vein thrombophlebitis.

CT pulmonary angiogram identified saddle embolism.

2D echocardiogram demonstrated a dilated, hypokinetic right ventricle with normal left ventricular function.

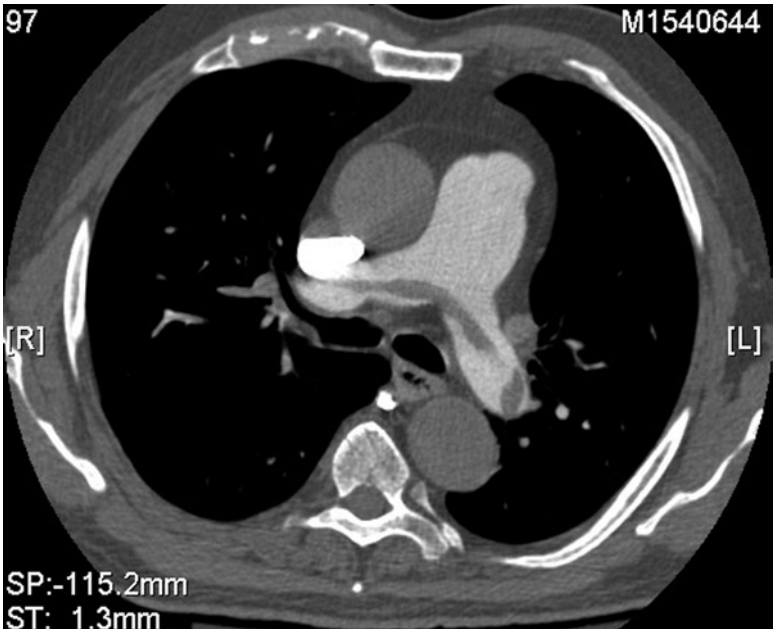

Fig. 12.2 CT pulmonary angiogram at the level of the bifurcation of the pulmonary artery demonstrates a saddle embolus lodged at the pulmonary artery bifurcation and entering both proximal main pulmonary arteries

What Is Your Diagnosis and Why?

In this case, pulmonary embolism was suggested by the acute onset of dyspnea and lower extremity edema in a patient at high risk for venous thromboembolism due to her age and history of breast cancer. The severity of the embolism was suggested by the presence of hemodynamic instability and transient atrial fibrillation. The patient's echocardiogram revealed a dilated, hypokinetic right ventricle with normal left ventricular function. The estimated pulmonary artery pressure was 50 mmHg. The patient suffered a saddle embolism as shown in Figs. 12.2 and 12.3. Both figures show that the embolus is lodged at the main pulmonary artery bifurcation and enters both the left and right pulmonary arteries. It is generally believed that, as in this case, saddle embolism is associated with hemodynamic instability and a poor prognosis. However, in a retrospective study of 546 pulmonary embolism patients only 14 (2.6%) had a saddle embolism [1]. Only 2 of the 14 saddle embolism patients had hypotension. It should be noted that none of the saddle embolism patients had preexisting cardiopulmonary disease. In a prospective study of 150 patients diagnosed with acute pulmonary embolism, a higher rate of saddle embolism was demonstrated (e.g. 22 patients or 14.7%) [2]. In spite of the fact that echocardiographic signs of right ventricular overload were more frequent in the saddle embolus patients, no statistical difference was demonstrated in mortality or complicated clinical course

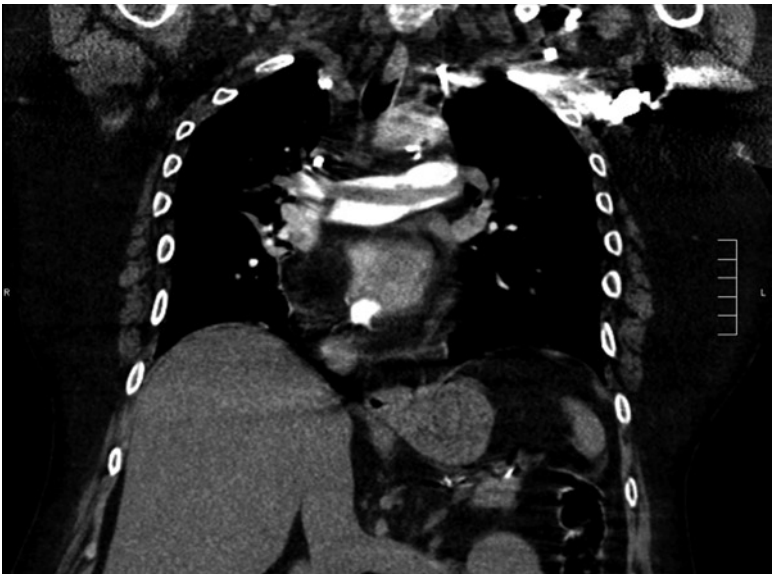

Fig. 12.3 A coronal reconstruction of the CT pulmonary angiogram at the level of the pulmonary artery bifurcation demonstrates the saddle embolus

for the saddle embolism group versus those without saddle embolism. These data suggest that saddle pulmonary embolism does not necessarily indicate an unfavorable clinical outcome. This patient was treated with tissue plasminogen activator, vena caval filter placement, enoxaparin, and then coumadin. Her hospital course was otherwise unremarkable.

Discussion

The pulmonary arterial circulation can be occluded by emboli composed of fat, amniotic fluid, air, tumor, foreign material (e.g., talc or methyl methacrylate), or thrombus. Infectious diseases (e.g., schistosomiasis, echinococcus) or hemoglobinopathies (e.g., sickle cell disease) may also result in pulmonary vascular occlusion. However, most pulmonary emboli originate in the deep venous vessels in the lower extremities. Other potential sources include the pelvic veins, inferior vena cava, renal veins, right ventricle, and upper extremity veins. The clinical signs and symptoms of pulmonary embolism are numerous, but most are nonspecific which can make diagnosis difficult. Acute pulmonary embolism can be classified as massive if it is associated with hypotension and submassive if it is not. With treatment, the endogenous plasmin system generally results in lysis of thrombi and restoration of normal pulmonary circulation. However, in some patients, the lytic system fails to adequately clear the pulmonary emboli. This results in chronic pulmonary vascular obstruction

and progressive increases in pulmonary vascular resistance. The patient experiences progressive exertional dyspnea that may be associated with chest pain over several years. Ultimately, these patients develop pulmonary hypertension and cor pulmonale. Treatment centers on empiric trial of prolonged anticoagulation with coumadin. If this fails then pulmonary endarterectomy may be undertaken if the patient is an appropriate surgical candidate.

The remainder of this chapter will review the incidence, natural history, pathophysiology, risk factors, signs and symptoms, diagnostic evaluation, and treatment of pulmonary embolism. Hypercoagulable states will also so be briefly discussed.

Incidence of Pulmonary Embolism

A retrospective review was performed of the complete medical records from a population-based inception cohort of 2,218 patients who resided within Olmsted County, Minnesota, and had an incident deep vein thrombosis or pulmonary embolism during the 25-year period from 1966 through 1990 [3]. The overall average age- and sex-adjusted annual incidence of venous thromboembolism was 117 per 100,000 (deep vein thrombosis, 48 per 100,000; pulmonary embolism, 69 per 100,000). As many as 300,000 patients die annually in the United States from embolism, and the diagnosis, unfortunately, is often not made until autopsy [4].

Pathophysiology/Natural History

Normally, microthrombi composed of platelets, small groups of red cells, and fibrin form and lodge in the lower extremity veins. This balance allows for adequate clotting to occur when necessary without pathologic clot propagation. Under certain circumstances, the balance can be tipped in favor of thrombus formation with subsequent formation of deep vein thrombi. Often, this thrombus formation begins in the venous valve cuffs or bifurcations that are prone to stasis. Lower extremity venous thrombosis generally begins in the calf veins, and about 20–30% of these calf vein thrombi will propagate into the proximal ileofemoral veins. The source of the majority of pulmonary emboli is from the proximal ileofemoral veins [5]. Thromboemboli can also arise from the pelvic, renal, or upper extremity veins, as well as the vena cava or right heart. About 79% of patient who present with pulmonary embolism have ultrasound evidence of lower extremity deep vein thrombosis [6]. In the remaining patients, it is likely that all of the thrombus in the lower extremity embolized prior to ultrasound examination. Pulmonary embolism occurs in about 50% of patients with proximal deep vein thrombophlebitis [7].

The clinical severity of pulmonary embolism depends to a large extent on the degree of obstruction of the pulmonary arterial vascular bed and the ability of the right ventricle to maintain left ventricular preload. Massive pulmonary embolism is

associated with shock. Massive pulmonary embolism should also be suspected in the presence of concurrent syncope or near syncope, hypotension, electromechanical dissociation, and cardiac arrest [4]. In general, a previously normal right ventricle is only able to generate and maintain a systolic pressure of 40–50 mmHg. If pulmonary vascular resistance increases further then the right ventricle will dilate, become hypokinetic, and, ultimately, stroke volume and cardiac output will fall. It should be noted that patients with preexisting cardiopulmonary disease may not tolerate even lesser degrees of clot burden. During acute pulmonary embolization, both vasoactive and bronchoactive substances are released such as serotonin and thromboxane A_2 that lead to worsening ventilation–perfusion mismatch.

Risk Factors

The classic conditions that predispose to the development of deep vein thrombophlebitis and pulmonary embolism have long been known as Virchow's triad: venous stasis, hypercoagulability, and venous injury or inflammation. Table 12.1 outlines the acquired conditions associated with increased risk of venous thromboembolism. Table 12.2 lists the currently known hereditary risk factors for venous thromboembolism.

At present, activated protein C resistance due to factor V Leiden is the most common genetic risk factor for venous thromboembolism. In general, the possibility of a hereditary cause for venous thromboembolism should be investigated in patients with thrombi in the absence of risk factors, younger patients, recurrent venous thromboembolism, family history of venous thromboembolism, and in patients with unusual sites of venous thrombosis (i.e., cerebral, mesenteric, hepatic, or portal) [4]. Most hypercoagulable states are associated with isolated venous thrombosis. Patients who develop both arterial and venous thrombosis should be evaluated for vasculitis, hyperhomocysteinemia, nephrotic syndrome, antiphospholipid antibody syndrome, cancer, chemotherapy, heparin-induced thrombocytopenia, paroxysmal nocturnal hemoglobinuria, polycythemia vera, and paradoxical embolization.

Signs and Symptoms

The prospective investigation of pulmonary embolism diagnosis II (PIOPED II) assessed the signs and symptoms of adult patients with and without prior cardiopulmonary disease being evaluated for possible pulmonary embolism [8]. Patients with shock were excluded. A total of 824 patients were included: 192 patients were documented to have acute pulmonary embolism and 632 did not have acute pulmonary embolism. The signs and symptoms of acute pulmonary embolism for patient with PE but no prior cardiopulmonary disease are noted below. The most common symptoms were dyspnea (rest or exertion) 73%, orthopnea 28%, pleuritic pain 44%, cough 34%, and calf or thigh pain 44%. In 72% of patients, dyspnea occurred acutely

Table 12.1 Acquired risk factors for venous thromboembolism

Strong risk factors
Leg or hip fractures
Hip or knee replacement
Major general surgery
Major trauma
Spinal cord injury
Other risk factors
Immobility
Malignancy
Chemotherapy
Prior venous thromboembolism
Advanced age
Pregnancy and the postpartum period
Estrogen containing contraceptives
Hormone replacement therapy
Selective estrogen receptor modulators
Polycythemia vera
Acute medical illness
Heart or respiratory failure
Inflammatory bowel disease
Nephrotic syndrome
Myeloproliferative diseases
Paroxysmal nocturnal hemoglobinuria
Obesity
Smoking
Varicose veins
Central venous catheters
Antiphospholipid antibody syndrome

Table 12.2 Hereditary risk factors for venous thromboembolism

• Antithrombin III deficiency
• Protein C deficiency
• Protein S deficiency
• Factor V Leiden
• Activated protein C resistance without factor V Leiden
• Prothrombin gene mutation (G20210A)
• Dysfibrinogenemia
• Plasminogen deficiency

(within seconds to minutes). The symptoms associated with acute pulmonary embolism included tachypnea (>20/min) 54%, tachycardia (>100/min) 24%, and calf or thigh pain 47%. Calf or thigh pain and swelling occurred more frequently in patients who had acute PE than those who did not. Fever, diaphoresis, and cyanosis were uncommon. Dyspnea, tachypnea, or pleuritic pain was present in 92% of patients. The absence of dyspnea did not exclude the diagnosis of pulmonary embolism.

Diagnostic Evaluation

Pulmonary embolism should be suspected in all patients presenting with new or worsening dyspnea, chest pain, pleuritic pain, and/or hemodynamic instability without an alternative obvious cause. The clinical presentation ranges from asymptomatic to shock state. Therefore, diagnostic evaluation begins with a careful history and physical examination, followed by evaluation of risk factors, and additional testing including D-dimer assay, electrocardiography, echocardiography, arterial blood gas analysis, and radiographic imaging (Fig. 12.4).

The clinical manifestations of both deep venous thrombosis and pulmonary embolism may be highly suggestive but are neither sensitive nor specific. Many of the clinical signs and symptoms are nonspecific. As discussed earlier, dyspnea, tachypnea, and pleuritic pain are the most common [8]. Often, the severity of symptoms depends on the degree of clot burden, but not always. For example, large peripheral thrombi may evolve silently and later present with symptoms; or smaller emboli may be associated with significant symptoms. Signs of pulmonary hypertension including elevated neck veins, a loud P2, a right-sided gallop, and a right ventricular lift may be present with cardiac strain. Thus, when pulmonary embolism is suspected, further testing must be considered [4].

Clinical-prediction scores are a useful tool in assessing the likelihood that a patient has an acute pulmonary embolism. They are based on information obtained from the history and physical examination. The two most commonly used are the Wells score and the Geneva score. Both are well validated in the evidence-based literature. Based on the result, either a low, moderate, or high pretest probability is determined [9, 10].

The D-dimer assay (which measures plasma levels of a specific derivative of cross-linked fibrin) is often part of the evaluation. Although a positive test may suggest venous thrombosis and pulmonary embolism, it is nonspecific, as it may be positive in patients with infection, malignancy, recent surgery, trauma, and other inflammatory states. When the D-dimer is negative in patients with low-moderate pretest probability, the likelihood of thromboembolic disease is low and precludes the need for imaging studies [4].

Further laboratory evaluation includes measurement of brain natriuretic peptide (BNP) and troponin. Elevated levels of either/both are nonspecific and insensitive. However, it has been shown that increased levels in the setting of pulmonary embolism portend an adverse outcome [11].

Arterial blood gas analysis usually identifies hypoxemia. Respiratory alkalosis is a classic finding. However, this may not always be seen. Hypoxemia can be minimal or absent. A PaO_2 between 85 and 105 mmHg exists in approximately 18% of patients with pulmonary embolism. Also, up to 6% of patients may have a normal alveolar-arterial oxygen gradient. An unexplained change in the arterial oxygen saturation should raise clinical suspicion [12].

Electrocardiography is useful but nonspecific. Abnormalities include unexplained sinus tachycardia. Manifestations of acute cor pulmonale, such as the classic S1Q3T3

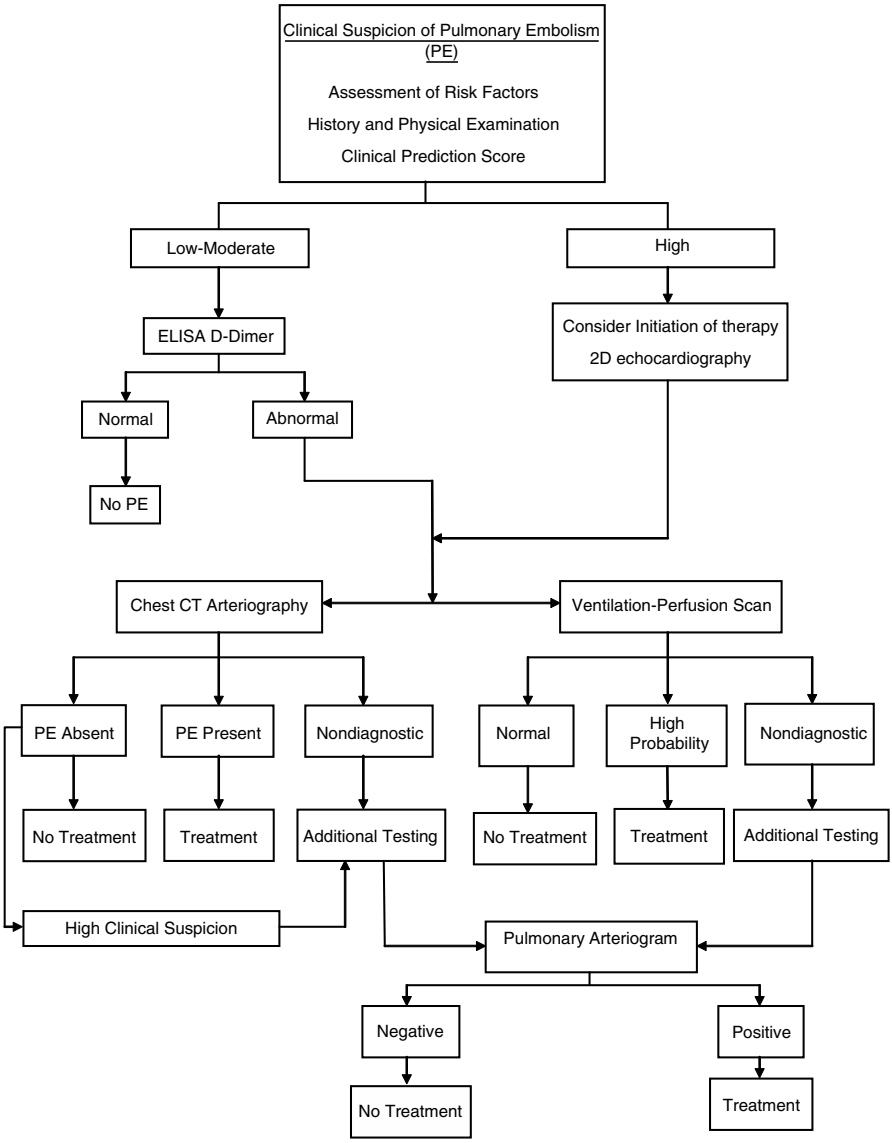

Fig. 12.4 Acute pulmonary embolism: diagnostic algorithm

pattern, p-wave pulmonale, right bundle branch block, or right axis deviation, are more common with extensive thromboembolic burden [13].

Echocardiography is essential in the evaluation. It may reveal right ventricular strain and/or hypokinesis strongly supporting hemodynamically significant pulmonary embolism. This immediately facilitates treatment especially when pharmacologic and/or mechanical thrombolysis is in question [11].

Radiographic imaging is the mainstay of the diagnostic evaluation. There are many types of imaging modalities available, including chest radiography, ventilation–perfusion scanning, contrast-enhanced computed tomographic arteriography (CTA), magnetic resonance angiography (MRA), and standard pulmonary arteriography. Imaging for deep venous thrombosis should also be undertaken. This may be with the use of ultrasonography, CT venography, MRI, or standard venography [4].

A chest radiograph is helpful primarily to rule out obvious causes of hypoxemia. In one study of 2,322 patients with pulmonary embolism, cardiomegaly was the most common radiographic abnormality. However, this finding did not correlate with right ventricular dysfunction by echocardiography [13].

CT arteriography is advantageous in not only the speed with which it can be obtained, but also in characterization of nonvascular structures and identification of venous thrombosis. CTA has a very high sensitivity and specificity for detecting emboli in the main, lobar, and segmental pulmonary arteries. In the PIOPED II trial, it was shown that the likelihood of pulmonary embolism in patients with a positive CT arteriogram and high, moderate, and low clinical probability was 96%, 92%, and 58%, respectively. The likelihood that pulmonary embolism was absent with a negative scan and a low, moderate, or high clinical probability was 96%, 89%, and 60%, respectively [14]. In a recent large, prospective trial conducted with outpatients with suspected acute pulmonary embolism, an excellent outcome was shown when anticoagulation therapy was not initiated after a negative chest CTA, which was the sole imaging study. However, in cases of high clinical suspicion, further imaging should be performed even if CT arteriography is negative [15].

A few trials have assessed combined CT arteriography and CT venography. The PIOPED II trial compared the use of multidetector CT arteriography alone with its use in combination with CT venography for detecting pulmonary embolism. The sensitivity of spiral CT arteriography alone was 83%, whereas with combined modalities it was 90%. This suggests that a combined approach may guide clinical management especially in complex cases [14].

Ventilation–perfusion scanning can be performed in situations where CT arteriography is prohibited. Such circumstances may include acute or chronic renal failure, or allergy to contrast material. A normal perfusion scan effectively rules out pulmonary embolism with a negative predictive value of 97%. A high-probability scan should be considered diagnostic (positive predictive value 85–90%) unless clinical suspicion is low or there is a history of previous pulmonary embolism with an identical scan. If the ventilation-perfusion scan is nondiagnostic, further testing must be pursued regardless of the degree of clinical suspicion [16].

The role of thoracic MRA in the diagnostic evaluation for pulmonary embolism is limited. Diagnosis is limited by respiratory and cardiac motion, and suboptimal resolution. In a prospective study of 118 patients with suspected embolism, MRA was compared to CT angiography. Overall, MRA was positive in 77% of patients with pulmonary embolism [17]. In the PIOPED III trial, MRA was recently shown to have insufficient sensitivity and a high rate of inadequate images when used for the diagnosis of pulmonary embolism [18].

Pulmonary angiography remains the "gold standard" in the diagnosis of acute pulmonary embolism. It is safe and well tolerated in the absence of hemodynamic compromise. Mortality from the procedure is less than 2%. Morbidity occurs in approximately 5% and is usually related to catheter insertion, cardiac arrhythmia, or respiratory failure. Radiation exposure is variable, but overall greater than CT arteriography. A negative pulmonary angiogram excludes clinically significant embolism [19].

Several diagnostic algorithms are available to guide evaluation [4, 11]. No approach has proven more beneficial than the others. Data from the Christopher study suggest algorithms can be effectively used [15]. Diagnostic evaluation begins with a clinical suspicion for pulmonary embolism. If suspicion is high, immediate therapy is considered, followed by chest radiography and CT arteriography or ventilation–perfusion scanning. If suspicion is low or moderate, a D-dimer assay is recommended. If the D-dimer is abnormal, workup ensues with the same radiographic imaging as the group with high suspicion. If the D-dimer is normal, no further workup is recommended. In populations where the prevalence of pulmonary embolism is low and the PE rule-out (PERC) criteria are met, further testing may be unnecessary [20].

Treatment

The treatment of pulmonary embolism centers around patient stabilization and anticoagulation. It is imperative that therapy be instituted quickly. Decisions regarding anticoagulation, pharmacologic or mechanical thrombolysis, and/or placement of inferior vena caval filter must be made (Fig. 12.5). The goals are to improve survivalship and prevent long-term sequelae such as post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension [4].

When pulmonary embolism is diagnosed, inpatient therapy is warranted. Bed rest for the first 24–48 h is recommended [4]. Initial focus is on achieving hemodynamic stability by providing supplemental oxygen, cautious intravenous fluid administration, and vasopressor therapy if needed, followed by anticoagulation.

Parenteral anticoagulation is the critical component of treatment. It has been shown to clearly improve survival among patients with symptomatic pulmonary embolism [21]. Subcutaneous low-molecular-weight heparin, subcutaneous fondaparinux, or weight-based intravenous unfractionated heparin should be administered, unless contraindicated, for at least 5 days, until the international normalized ratio is in the therapeutic range (2.0–3.0) for 2 consecutive days. Oral vitamin K antagonists, such as warfarin, can be initiated on the first day of therapy. Although no evidence-based recommendations for the treatment of isolated subsegmental pulmonary emboli can be made, they are generally treated [4].

Low-molecular-weight heparin has advantages over unfractionated heparin, including longer half-life, greater bioavailability, predictable dosing, subcutaneous delivery, and lower risk of heparin-induced thrombocytopenia. However, it should not be used in patients with severe renal insufficiency. Randomized trials support the use of low-molecular-weight heparin as monotherapy. It may, in fact, be superior to

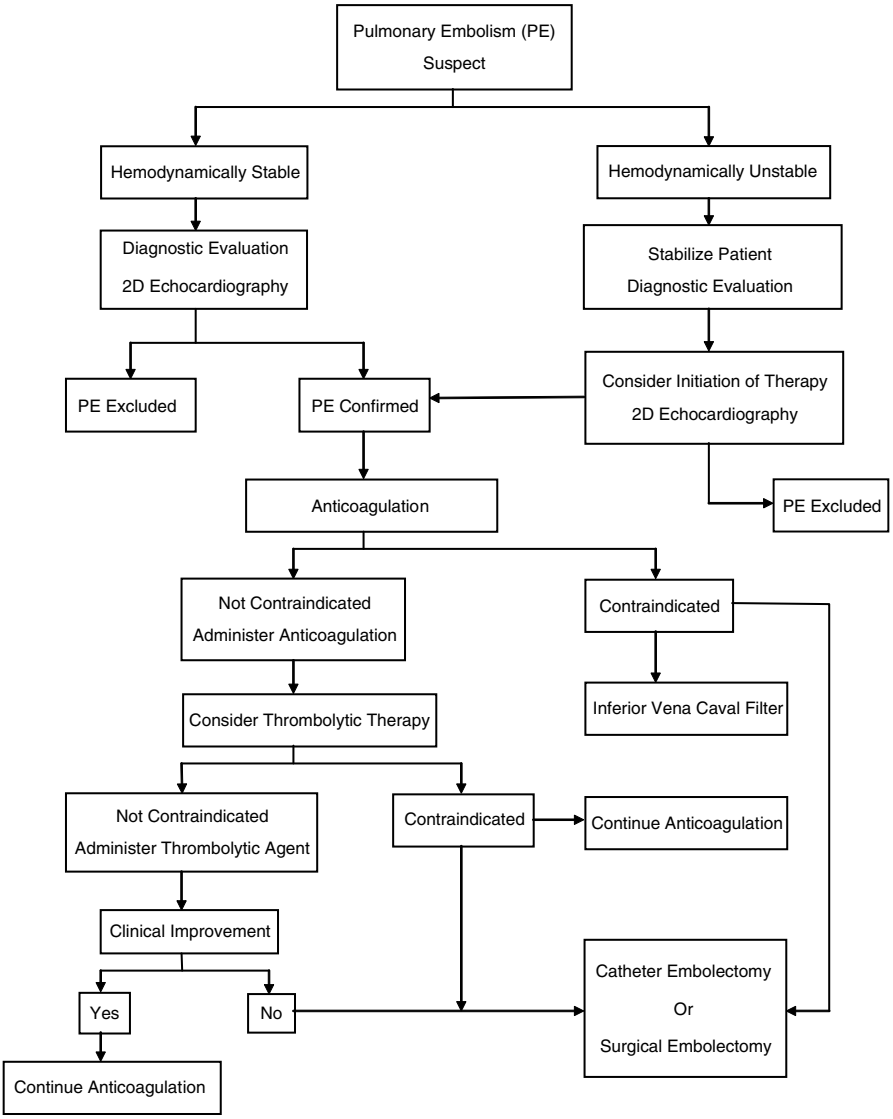

Fig. 12.5 Acute pulmonary embolism: treatment algorithm

unfractionated heparin for deep venous thrombosis, and at least as effective as unfractionated heparin in reducing the risk of death and the risk of major bleeding during initial therapy for pulmonary embolism [22]. In patients with acute nonmassive pulmonary embolism, the American College of Chest Physicians recommends the use of low-molecular-weight heparin rather than standard heparin [21]. In patients with massive pulmonary embolism, if thrombolytic therapy is being considered, intravenous unfractionated heparin is the recommended form of initial anticoagulation.

It is withheld during administration of the fibrinolytic agent and then restarted when the activated partial thromboplastin time has fallen to less than twice the upper limit of normal [23].

Fondaparinux is a synthetic pentasaccharide with anti-Xa activity approved by the FDA for the initial treatment of venous thromboembolism including pulmonary embolism. In hemodynamically stable patients with acute symptomatic pulmonary embolism, fondaparinux is as safe and effective as intravenous unfractionated heparin. Advantages include fixed dosing and no risk of heparin-induced thrombocytopenia. It should not be used in patients with renal insufficiency [23].

Treatment with a direct thrombin inhibitor, such as argatroban or lepirudin, should be considered for heparin-induced thrombocytopenia with thrombosis. Treatment with warfarin should not be initiated until the disease process has been controlled and the platelet count has returned to normal because of the potential for thrombotic complications including venous limb gangrene and warfarin-induced skin gangrene [4].

Thrombolysis, either pharmacologic or mechanical, must be considered in proven pulmonary embolism causing hemodynamic compromise. Therapy is considered not only for those patients with cardiogenic shock, but also in those with systemic hypotension without shock. The use of thrombolysis in the setting of right ventricular dysfunction without hypotension is debated as there is insufficient clinical data to support survival benefit in this situation [4]. Pharmacologic thrombolysis has been shown to be associated with a more rapid resolution of thromboembolic obstruction and right ventricular dysfunction as compared to anticoagulation alone. However, at week 1, the degree of clot lysis and right ventricular dysfunction was similar [11]. Catheter-based mechanical pulmonary embolectomy or surgical embolectomy is considered when there are contraindications and/or complications from pharmacologic thrombolysis. Additional indications for open surgical embolectomy include paradoxical embolism, persistent right heart thrombi, and hemodynamic compromise requiring cardiopulmonary resuscitation [23]. No clinical trial has been large enough to conclusively demonstrate a mortality benefit. Therefore, clinical judgment weighing the risks and benefits of thrombolytic therapy is imperative.

Indications for the placement of an inferior vena caval filter include contraindications to anticoagulation, major bleeding during anticoagulation, embolism despite adequate anticoagulation, and those undergoing open surgical embolectomy. Filters are often placed when it is believed that the risk of additional emboli might be fatal, such as in the case of massive pulmonary embolism, particularly if pharmacologic or mechanical thrombolysis is contraindicated. However, this latter indication has not been studied in randomized prospective clinical trials. Inferior vena caval filters are effective in reducing the incidence of pulmonary embolism, but they have been shown to increase the risk of subsequent thrombosis and have not been shown to increase overall survival [4].

Documented thromboembolism in patients with transient risk factors should be treated for 3–6 months. Recent data suggest that D-dimer levels may help guide decisions about the duration of therapy. Persistently elevated levels appear to be associated with an increased recurrence rate [4]. Those with persistent risk factors for venous

thromboembolism, recurrent embolism, hypercoagulable state, immobilization, and/or malignancy require indefinite therapy. Patients should also be monitored for long-term sequelae, such as chronic thromboembolic pulmonary hypertension, as the incidence at 2 years ranges from 0.8% to 3.8% [11].

Questions

1. Which of the following is not a major risk factor for venous thromboembolism?

   (a) Recent major abdominal surgery
   (b) Postpartum state
   (c) Recent fall
   (d) Malignancy
   (e) Chemotherapy

2. Which of the following is associated with both arterial and venous thromboembolism?

   (a) Lupus anticoagulant
   (b) Protein C deficiency
   (c) Protein S deficiency
   (d) Factor V Leiden mutation
   (e) Antiphospholipid antibody

3. Which patient should not receive indefinite anticoagulation?

   (a) Hypercoagulable state
   (b) Recurrent DVT/PE
   (c) Malignancy
   (d) Massive pulmonary embolism
   (e) Postsurgical DVT/PE

4. Which of the following is not an indication for inferior vena caval filter placement?

   (a) Massive pulmonary embolism
   (b) Recurrent DVT/PE on adequate anticoagulation
   (c) Fall risk
   (d) Complications/contraindications to anticoagulation
   (e) First idiopathic DVT/PE

5. Which of the following is not a complication of acute pulmonary embolism?

   (a) Pulmonary infarction
   (b) Pulmonary hemorrhage
   (c) Chronic thromboembolic pulmonary hypertension
   (d) Development of vasculitis
   (e) Death

6. The two most helpful diagnostic tests in the evaluation of pulmonary embolism are:

   (a) CT chest arteriography and 2D echocardiography
   (b) Pulmonary arteriogram and venous ultrasonography
   (c) Ventilation–perfusion scan and venous ultrasonography
   (d) D-dimer and CT chest arteriography
   (e) Thoracic MRA and 2D echocardiography

7. The "gold standard" diagnostic test for pulmonary embolism is:

   (a) CT chest arteriography
   (b) Pulmonary angiogram
   (c) 2D echocardiography
   (d) Ventilation–perfusion scan
   (e) Thoracic MRA

8. The duration of treatment for first episode of idiopathic DVT/PE is:

   (a) 3–6 months
   (b) 9 months
   (c) 12 months
   (d) 18 months
   (e) Indefinite therapy

9. Which of the following is not true regarding thrombolysis for acute pulmonary embolism are:

   (a) It is indicated for massive pulmonary embolism with hemodynamic instability
   (b) Pharmacologic thrombolysis in the setting of embolism with right ventricular dysfunction but without hypotension has been shown to improve survival
   (c) Catheter or surgical embolectomy is considered when there are contraindications and/or complications from pharmacologic thrombolysis
   (d) There is no conclusive mortality benefit
   (e) Pharmacologic thrombolysis has been shown to result in more rapid resolution of thromboembolic obstruction compared to anticoagulation alone

10. Which of the following is true regarding saddle pulmonary embolism?

    (a) It is usually associated with significant hemodynamic compromise
    (b) It portends an unfavorable outcome
    (c) The majority of patients present with hypotension
    (d) All of the above
    (e) None of the above

Answer key: 1. (c), 2. (e), 3. (e), 4. (e), 5. (d), 6. (a), 7. (b), 8. (a), 9. (b), 10. (e)

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Chapter 13
Pulmonary Vasculitis Conundrums

Matthew Sisitki and Samuel Louie

Abstract Pulmonary vasculitides represent a diverse group of diseases typified by nonspecific signs and symptoms with evidence of systemic extra-pulmonary organ involvement, including skin, kidney, and neurological systems. No single confirmatory diagnostic laboratory test exists; therefore the clinician must combine a thorough history and physical examination with other objective findings to make the correct diagnosis.

Keywords Pulmonary-renal syndrome • Diffuse alveolar hemorrhage • Anti-nuclear cytoplasmic antibodies • Vasculitis • Microscopic polyangiitis syndrome • Churg–Strauss syndrome • Wegner granulomatosis

Case 1

A 38-year-old man was admitted to hospital for acute renal failure and multiple pulmonary nodules on chest X-ray. He had recently complained of migratory arthralgias and myalgias over the prior 2 weeks with subjective fevers, chills, and night sweats, and taking about 16 tablets of ibuprofen daily to control pain. Two months earlier, he was admitted to another hospital for 3 days complaining of bilateral diminished hearing, otorrhea, and left facial droop. He was diagnosed with a severe sinus infection with reported bone involvement and responded to intravenous antibiotics and corticosteroids. He was discharged with a 1-week course of levofloxacin.

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No kidney abnormalities or abnormal chest X-ray during the hospitalization was mentioned. An occasional dry cough persisted, attributed to postnasal drip.

Review of systems was negative for skin rashes, joint swelling, sore throat, changes in bowel movements, dysphagia, odynophagia, back pain, changes in his urination, or hematuria. He endorsed some weight loss – approximately 10 lb – over the past 3 months from diminished appetite.

A history of Factor VIII deficiency was elicited; however, he had never required factor replacement and never had hemarthrosis. In addition to a job as a restaurant manager, the patient also worked as a stagehand at music concerts. He was frequently exposed to dusty environments while working backstage, but denied exposures to organic or mineral dusts, or to any fumes or gases at work. He currently smokes and has a 20-pack-year history. He denied owning any pets, but his mother whom he visits 3–4 times a year has exotic birds. He was born in the United States and has not traveled outside of the country. Family history includes Factor VIII deficiency in his maternal grandfather, who also had lung cancer.

He was a normal-appearing man in no distress. His temperature was 37°C, blood pressure 129/80 mmHg, pulse 98 beats/min, and respiratory rate 18 breaths/min. Oxygen saturation on room air was 100% by pulse oximeter. His pupils were equal and reactive to light bilaterally. Oropharynx was normal in appearance without any ulcers, thrush, petechiae, or other lesions. Dentition was good. Neck was supple without thyromegaly, palpable lymphadenopathy, or masses. The trachea was midline and mobile. No heart murmurs, rubs, or gallops were auscultated. Clear breath sounds with good air movement was auscultated bilaterally without dullness to percussion. Abdominal and genitourinary examinations were unremarkable, without hepatosplenomegaly or testicular masses. No skin lesions, clubbing, or edema were found on extremities. No joint abnormalities or tenderness was evident. Muscle groups proximally and distally were nontender.

A serum creatinine of 4.29 mg/dL was found on initial laboratory testing. The remainder of his chemistry panel and liver function tests were within normal limits except for an albumin of 2.3 g/dL. Partial thromboplastin time (PTT) was elevated at 39.4 s. Factor VIII was present at lower levels than normal human plasma at 26%. Complete blood count (CBC) and urinalysis results are displayed in Tables 13.1 and 13.2, respectively, and chest X-ray in Fig. 13.1.

Initial Impressions

What Is Your Working Diagnosis?

Acute renal failure with red-cell casts is highly suggestive of glomerulonephritis. Combined with discreet lung nodules and recent history of sinus-related symptoms, a pulmonary-renal syndrome should be considered, including Wegener granulomatosis (WG). Nonspecific sinus symptoms can precede renal and pulmonary involvement for years in WG. Other vasculitides such as Goodpasture syndrome

Table 13.1 Complete blood count

WBC (4.5–11 k/mm^3)	12.7	Neutrophils%	71.8
Red Cell Count (4.5–5.9 m/mm^3)	3.40	Lymphocytes%	13.8
Hgb (14–18 g/dL)	9.1	Monocytes%	10.4
HCT%	27.3	Eosinophils%	3.2
MCV (80–100 um^3)	80.3	Basophils%	0.8
MCH (27–33 pg)	26.6	Neutrophil Abs (1.8–7.7 k/mm^3)	9.10
MCHC (32–36%)	33.2	Lymphocytes Abs (1.0–4.8 k/mm^3)	1.8
RDW (0–14.7 units)	14.8	Monocyte Abs (0.1–0.8 k/mm^3)	1.3
MPV (6.8–10 um^3)	7.1	Eosinophil Abs (0–0.5 k/mm^3)	0.4
Platelet (130–400 k/mm^3)	760	Basophils Abs (0–0.2 k/mm^3)	0.1

Table 13.2 Urinalysis

Color	Yellow	Urobilinogen	Negative
Clarity	Clear	Nitrite	Negative
pH (4.8–7.8)	5.0	Leukocyte Est.	Negative
Specific gravity (1.002–1.030)	1.010	Bacteria/HPF	Few
Occult blood	Large	WBC (0–3/HPF)	7
Bilirubin	Negative	RBC (0–6/HPF)	38
Ketones	Negative	Squamous Epi.	<1
Glucose	Negative	RBC casts	1
Protein	50 mg/dL	Granular casts	1
Sulfosal	Positive	Mucus/LPF	Few

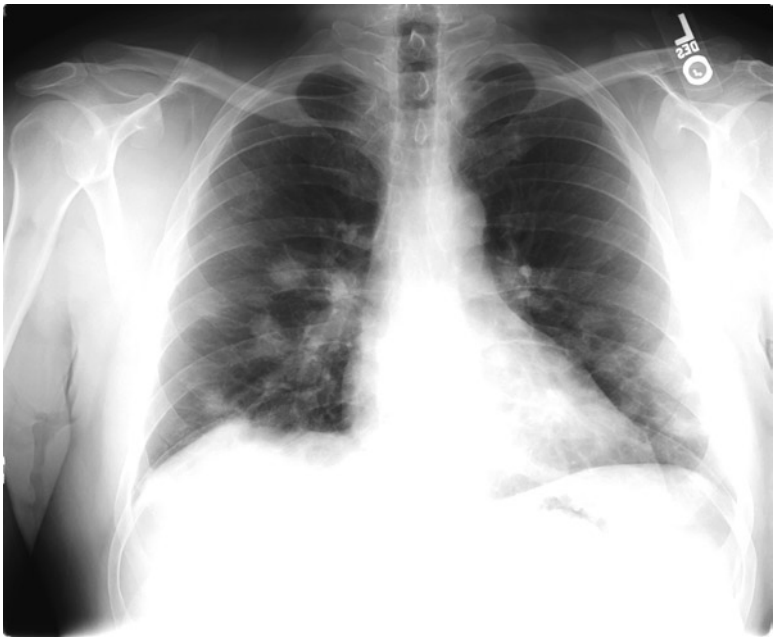

Fig. 13.1 Case 1 Chest X-ray

with anti-glomerular basement membrane (anti-GBM) antibodies, microscopic polyangiitis (MPA), Churg–Strauss syndrome (CSS), and systemic lupus erythematosus (SLE) are more likely to cause diffuse alveolar hemorrhage (DAH) rather than bilateral lung nodules.

The patient's heavy use of nonsteroidal, antiinflammatory drugs could explain the renal failure although red-cell casts would be atypical. Glomerulonephritis can occur during infection as in IgA nephropathy or in delayed fashion as in postinfectious glomerulonephritis. Acute and subacute endocarditis could injure the kidney and produce pulmonary nodules via septic emboli. Cavitary nodules would be expected in endocarditis; however, the absence of this finding on chest X-ray does not exclude the possibility.

Other lung infections can cause the radiographic appearance of masses and nodules in the lung. Coccidioidomycosis, histoplasmosis, and blastomycosis are soil-dwelling fungi that may cause lung disease in endemic areas. This patient's exposure history is only supportive of coccidioidomycosis, but *Mycobacterium tuberculosis* (TB) should be included in the differential given its predilection to atypical presentations and multiple organ involvement. *Aspergillus* species, ubiquitous in the environment, is unlikely to cause discreet lung nodules and generally only cause invasive infection in immunocompromised individuals. Other possibilities could include nocardia, actinomyces, and cryptococcus, but again these are less common in immunocompetent people. Parasitic diseases such as schistosomiasis, paragonimiasis, and cysticercosis are unlikely without travel to endemic areas.

Primary lung cancer or metastatic cancer, as well as lymphoma can cause discrete nodules in the lung, although no significant mediastinal lymphadenopathy is suggested by the chest X-ray and no enlarged nodes were found on examination. The possibility of renal cell carcinoma should not be overlooked given the combination of hematuria and lung nodules. Testicular cancer is unlikely given the normal genitourinary exam, but is not completely excluded by a normal examination.

Sarcoidosis, specifically of the nodular type, is possible. Renal failure can occur in sarcoidosis due to altered vitamin D metabolism and subsequent hypercalciuria with stone formation invoking renal injury. Again, the finding of red-cell casts argues for glomerulonephritis rather than other causes of renal failure.

Differential Diagnosis

1. Pulmonary-Renal syndromes (WG, MPA, Goodpasture, SLE)
2. NSAID-induced nephropathy, post-infectious glomerulonephritis, IgA nephritis
3. Malignancy (metastatic cancer, primary lung cancer, lymphoma, renal cell carcinoma)
4. Infection (fungal pneumonia, TB, endocarditis)
5. Sarcoidosis

Table 13.3 Immunologic tests

Complement C3 (92–210 mg/dL)	154
Complement C4 (14–49 mg/dL)	42
Anti-neutrophil cytoplasmic antibodies C	1:160
Anti-neutrophil cytoplasmic antibodies P	Negative
Myeloperoxidase antibody (0–19 AU/mL)	0
Serine protease 3 antibody (0–19 AU/mL)	630
Anti-nuclear antibody	Negative
Anti-DNA antibody	Negative
Anti-glomerular basement membrane antibodies	Negative
Antistreptolysin titer (0–330 IU/mL)	<55

Workup

An immunologic and infectious disease workup was initiated on based on the differential diagnosis (Table 13.3). Blood cultures were drawn and no growth was found. Serologies for *Aspergillus* galactomanin, coccidioides, blastomyces, and histoplasmosis were negative, as was histoplasmosis urine antigen. A quantiferon-gold assay was also negative. Cryptococcal serum antigen was negative. A viral hepatitis panel was negative. HIV antibody assay was nonreactive. Chest computed tomography (CT) demonstrated multiple variably-sized pulmonary nodules with rare areas of possible cavitation and mild mediastinal adenopathy (Fig. 13.2). An echocardiogram was normal and did not show any valvular abnormalities or vegetations.

Kidney biopsy was performed. Pathologic diagnosis was pauci-immune crescentic glomerulonephritis. Thoracic surgery was consulted and performed a lung-wedge biopsy of the left lower lobe. Lung pathologic findings demonstrated nodules of necrotizing granulomatous inflammation, interpreted as atypical for WG with no vasculitis or malignant cells seen. Stains for fungal and acid-fast (AFB) organisms were negative. Bacterial, fungal, and acid-fast bacilli tissue cultures from the lung biopsy did not demonstrate organisms on microscopic review nor on culture.

What Is Your Final Diagnosis and Why?

Pulmonary-Renal Syndrome Due to Wegener Granulomatosis

Our patient presented with acute renal failure, microscopic hematuria and red-cell casts, and pauci-immune crescentic glomerulonephritis on kidney biopsy. Although other etiologies of the renal failure were considered during the initial evaluation, the finding of rapidly progressive glomerulonephritis argues against NSAID-induced nephropathy and post-infectious nephritis. The absence of immune complexes on kidney biopsy excludes IgA, Goodpasture syndrome with anti-GBM antibodies, and SLE. The pauci-immune pattern is most often associated with antineutrophil cytoplasmic antibody (ANCA) vasculitides such as WG, MPA, and CSS.

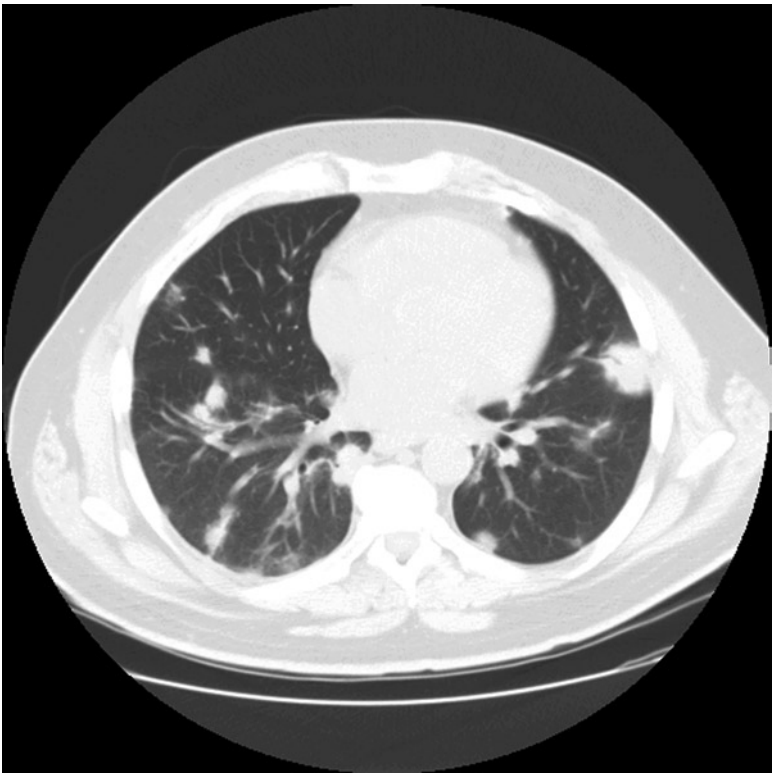

Fig. 13.2 Case 1 Chest CT

The evaluation of the patient's lung nodules did not suggest an infectious cause nor did his clinical history, serologic and culture tests results, and most importantly, lung biopsy. Similarly, no malignancy was found on pathologic investigation.

The immunologic tests strongly support the diagnosis of WG. Our patient was found to have a positive cytoplasmic ANCA (C-ANCA) with a very elevated serine protease-3 antibody (PR3). Negative antinuclear antibodies (ANA) and normal complement levels, as well as a negative perinuclear ANCA (P-ANCA) point away from SLE and MPA, respectively. Both of these entities are more likely to cause DAH rather than nodular patterns in the lung, and one would expect other exam findings with a systemic disease such as lupus. CSS is another small vessel, necrotizing vasculitis that can present with glomerulonephritis, sinusitis, constitutional symptoms, and many other similar clinical features to WG. CSS is strongly associated with elevated levels of myeloperoxidase (MPO) and P-ANCA, in addition to severe persistent asthma, mononeuritis multiplex, peripheral eosinophilia, and eosinophilic pneumonia, which were not evident in this case.

Necrotizing granulomas can be found in a variety of diseases that affect the lung other than WG, including CSS, infections, sarcoidosis, hypersensitivity pneumonitis,

and drug toxicity. The lung biopsy in this patient exhibited necrosis somewhat atypical of WG and no vasculitis was noted. However, taking the patient's constellation of findings into account, specifically positive C-ANCA and PR3 tests, pauci-immune crescentic glomerulonephritis, multiple lung nodules without evidence of infection or malignancy, and a history not supportive of toxic medication or hypersensitivity, WG is the most likely diagnosis.

Discussion

Wegener Granulomatosis is a systemic disease characterized by necrotizing granulomas and a small- to medium-sized vasculitis. The syndrome was first recognized as early as 1931, but later described in case series by Wegener in 1936 [1]. It has an equal prevalence among men and women although its overall incidence is low, estimated at 10–20 cases per million people [2]. The disease is primarily seen among Caucasians, representing about 98% of all cases, and the typical age of onset is in the fourth or fifth decade of life [1, 3].

Although known as a pulmonary-renal syndrome for its predilection to respiratory and kidney involvement, the idiopathic necrotizing granulomas and vasculitis of WG can affect any organ system [4]. The classic clinical triad of upper airway disease, lung involvement, and glomerulonephritis may not always be present in every patient. The respiratory tract, both upper and lower, is the most commonly affected in 85% of cases [1]. Upper respiratory tract symptoms can precede more severe pulmonary presentations of disease for years, manifesting as sinusitis, otitis, rhinitis, epistaxis, and sensorineural hearing loss, among other symptoms [5]. Hoarseness, chronic cough, or wheezing may occur with tracheal involvement either from inflammation or subglottic tracheal stenosis. Lower respiratory tract symptoms can range from mild cough or dyspnea to severe hemoptysis and respiratory failure depending on the degree and location of involvement. Some patients may experience no pulmonary symptoms at all despite the finding of an abnormal chest X-ray [4].

Only about one-fifth of cases have evidence of renal involvement at initial presentation; however, glomerulonephritis eventually develops in about 80% [1, 6]. Lack of kidney disease should therefore not dissuade one from the diagnosis. Hematuria, nephritis, and renal failure are typical. Constitutional signs and symptoms of fevers, arthralgias, myalgias, weight loss, and fatigue are frequent patient concerns. Nearly half of patients have vasculitic skin changes or subcutaneous nodules. Scleritis, keratitis, optic neuritis, and vein occlusion are just some of the many ocular phenomena. Neuropathy, headaches, and cerebral vasculitis are documented, but are less common [1, 4, 5].

No defining clinical guideline exists for the diagnosis of WG and no single test is pathognomonic. A thorough history and meticulous physical examination is therefore paramount in discerning WG from other vasculitides and other diseases that may present similarly. When unexplained or unresponsive pulmonary, sinus, or neurologic symptoms are present, the diagnosis of WG should be entertained.

The chest X-ray may show diffuse, variably-sized nodules, with or without cavitation. Areas of localized ground glass infiltrates representative of hemorrhage may be present. The pulmonary-edema like pattern seen with DAH is described in severe cases, but is infrequent. Laboratory studies may demonstrate leukocytosis, anemia, or thrombocytopenia. Markers of inflammation such as the erythrocyte sedimentation rate and the C-reactive protein are likely to be elevated in active disease. With kidney involvement, active urine sediment with red-cell casts, crenated red cells, and non-nephrotic range proteinuria may be detected, along with an elevated serum creatinine when renal failure is present [4–6].

The ANCA tests can be of great value in supporting the diagnosis of the small-vessel vasculitides. Antinuclear cytoplasmic antibodies immunofluorescence assays detect specific C-ANCA or P-ANCA patterns that are generated from antibodies binding to PR3 and MPO antigens, respectively. Enzyme-linked immunosorbent assays (ELISA) are directed to the PR3 and MPO antigens and detect binding of antibody-antigen complexes. Sensitivity of these tests is reported quite variably, ranging from less than 50% to greater than 90%. This is likely a consequence of samples determined at different time points and at different severities of disease. When tested during active disease and with a high clinical pretest probability, they are highly sensitive tests (85–95%), emphasizing the importance of a diligent history and physical examination. Specificity of the tests is also very high, generally reported at 95–99%. About 24% of WG will have dual positivity with P-ANCA/MPO, and about 27% of MPA will have positive C-ANCA [3–6].

Though a confident diagnosis of WG may be made based on laboratory studies, history, and physical examination, all of these features remain only supportive rather than confirmatory. Additionally, the treatment for WG entails an intense regimen of immunosuppressive therapy with corticosteroids and cyclophosphamide, often for a long duration, making exclusion of infection, malignancy, and other causes of paramount importance. Tissue biopsy is necessary in the majority of cases [4]. WG can affect nearly any organ system, but in most cases the histologic findings from skin, kidney, or nose may not reveal diagnostic necrotizing granulomas and small vessel vasculitis. Biopsy of skin lesions is of low yield, often demonstrating nonspecific changes. The majority of sinus and throat biopsies show only inflammatory changes and are diagnostic in only about 20% of specimens. Kidney biopsy may be indicated to discern the etiology of renal failure, but diagnostic granulomas are rarely seen [1, 4, 5]. Specimens revealing pauci-immune glomerulonephritis aid greatly in narrowing the differential diagnosis, but this is only supportive and not confirmatory [6]. Open lung biopsy offers the highest yield in WG. Transbronchial lung biopsies are of very low yield, positive in only about 7–10% of cases [1, 5]. This is likely due to the small samples obtained and the patchy nature of the lung involvement. Bronchoscopy may help exclude other causes (i.e., bronchoalveolar lavage for eosinophilia, biopsies, and/or CD4/CD8 ratio for sarcoidosis, etc.), and can confirm DAH. Fine-needle aspiration lung biopsy is also very unlikely to provide diagnosis because of the small sample size. Open-lung biopsy is ultimately necessary in a majority of cases, with histologic staining and cultures to exclude infection and malignancy. Diagnostic sensitivity is around 91% [1, 4, 5]. The heterogeneity of lung nodules at different stages and the irregular distribution along with variable

presentation of severity at disease presentation can cause uncertainty even after large tissue samples are obtained. As in our case, the diagnosis of WG is based on a combination of key supportive features and lack of other disease entities and not on any single piece of data.

Left untreated, WG is associated with high morbidity and mortality. Prior to the use of immunosuppressive therapies for WG, mortality was estimated at 75% with a median survival of 5 months. Severe presentations of the disease can progress rapidly to death from acute renal failure or acute respiratory failure. Relapse occurs in about 50% of cases and morbidity from pharmacologic therapy can be serious. Early diagnosis and initiation of treatment can have a significant impact on outcome, lowering mortality rates at 5 years to 12% [1, 4, 7].

Intensity of therapy is based on disease severity, but consensus guidelines have not been agreed upon. The European Vasculitis Study Group (EUVAS) classification of disease severity is often used as a guideline for the start of induction therapy (Table 13.4). Localized or early systemic WG may be treated with a combination of systemic corticosteroids and methotrexate. More aggressive presentations of disease with threat or evidence of renal or other organ injury are treated with combination corticosteroids plus cyclophosphamide until significant remission of disease is achieved [6]. Plasmapheresis is recommended with severe or life-threatening disease and may improve outcomes in renal function although it has not been shown to improve overall mortality. Plasmapheresis is also recommended for DAH based on outcomes with Goodpasture syndrome and in smaller studies with the ANCA vasculitides, but remains unconfirmed in controlled trials [1, 7]. Once control of disease has been achieved for 6–9 months, maintenance therapy is started with azathioprine or methotrexate added to corticosteroids. Recent trials with rituximab as an induction agent have shown non-inferiority to cyclophosphamide, but due to confounding factors in the studies the question remains open. Other agents, including IV immunoglobulins (IV IG) and tumor necrosis factor-α targeting agents, are under continued investigation [7].

There can be significant pressure to initiate treatment when the diagnosis of WG is being considered. The conscientious clinician must weigh the risk of delaying treatment against starting immunosuppressive therapy when infection has not been fully excluded. To preserve or salvage renal function in our patient, systemic corticosteroids were given once the WG diagnosis was fairly certain, and cyclophosphamide was only started 3 days later after the lung biopsy failed to demonstrate an infectious cause. The benefits of systemic corticosteroids outweighed the potential risk of immunosuppression and worsening infection. The logic being that although corticosteroid therapy could worsen an infection, the effects would be shorter lived than had cyclophosphamide therapy been started and then stopped.

Case 2

A 31-year-old woman was transferred from an outside hospital for frank hemoptysis and renal failure. She was 8-weeks postpartum and had undergone a cesarean section at 38-weeks gestation for pre-eclampsia. Hospitalization was preceded by a 2-week

Table 13.4 European Vasculitis Study Group Grading of Disease

	Definition	Constitutional Symptoms	Renal Function	Threatened Organ Function	Treatment
Localized	Upper and/or lower respiratory tract disease without other systemic involvement	No	Creatinine <1.4 mg/dL	No	Glucocorticoids +/− methotrexate
Early Systemic	Any, without organ-threatening or life-threatening disease	Yes	Creatinine <1.4 mg/dL	No	Glucocorticoids and methotrexate
Generalized	Renal or other organ threatening disease	Yes	Creatinine <5.6 mg/dL	Yes	Cyclophosphamide and glucocorticoids
Severe	Renal or other vital organ failure	Yes	Creatinine >5.6 mg/dL	Yes	Cyclophosphamide and glucocorticoids, plasmapheresis
Refractory	Progressive disease unresponsive to glucocorticoids and cyclophosphamide	Yes	Creatinine >5.6 mg/dL	Yes	Investigational agents

prodrome of cough with scant hemoptysis and shortness of breath that progressively worsened to coughing up large blood clots. In the same period, she also noted the onset of gross hematuria.

On review of systems, she denied any fevers, chills, night sweats, headache, chest pain, skin rashes, focal weakness, paresthesias, dysuria, myalgias, or arthralgias. Her previous pregnancy was accompanied by hematuria, but she did not seek medical evaluation. The patient believed her menstrual cycles had returned since her pregnancy. Her only medication was iron sulfate. No new medications were prescribed in the months prior to admission.

Her past medical history included asthma since childhood. She had never been hospitalized for breathing difficulty. She uses her rescue albuterol inhaler 2–3 times per week and did not experience nighttime awakenings due to asthma. She has been pregnant four times and has four children, three of which were delivered by cesarean sections. During her second pregnancy, she had placenta previa. No history of tuberculosis or occupational exposure was solicited, and she denied smoking tobacco and illicit drug use. She had no pets in her home or frequent animal exposures. She was born in the United States and had never lived overseas, nor did she travel recently.

Her general appearance was significant for mild to moderate labored breathing. Her temperature was 36.4 C, pulse 80 beats/min, blood pressure 134/76 mmHg, and respiratory rate 18 breaths/min. Pulse oximetry was 96% on supplemental oxygen 2 L/min by nasal cannula. Head, neck, and oral examinations were normal including no petechiae or skin ulcers. There was no palpable cervical lymphadenopathy. Heart examination was normal. Lung auscultation revealed bilateral wheezes with inspiratory and expiratory crackles. No dullness to percussion or egophony was found. Abdominal exam was unremarkable, with no hepatosplenomegaly or palpable masses. There was a healing cesarean incision. Both lower extremities had 1 mm of pitting edema. There was no thickening, tenderness, or stiffness of the joints on her hands. Muscle groups were nontender.

Early laboratory results are summarized in Tables 13.5–13.7 and the chest X-ray in Fig. 13.3. Liver function tests, INR, and PTT were all within normal limits.

Impression

What Is Your Working Diagnosis?

This patient presented with subacute onset of hemoptysis, acute renal failure, anemia, and diffuse airspace infiltrates on chest X-ray. Urinalysis showed hematuria with signs of renal tubular and or glomerular injury demonstrated by cellular and granular casts.

Hemoptysis is not uncommon with bronchopneumonia. Acute renal failure from acute tubular necrosis (ATN) is frequent in the critically ill patient with sepsis. Infectious etiologies are of immediate concern. Any bacterial pneumonia can be

Table 13.5 Complete blood count

WBC (4.5–11 k/mm^3)	7.1	Neutrophils%	88
Red cell count (4.5–5.9 m/mm^3)	2.86	Lymphocytes%	6.7
Hgb (14–18 g/dL)	8.2	Monocytes%	4.7
HCT%	24	Eosinophils%	0.3
MCV (80–100 um^3)	84	Basophils%	0.3
MCH (27–33 pg)	28.6	Neutrophil Abs (1.8–7.7 k/mm^3)	11.20
MCHC (32–36%)	34.1	Lymphocytes Abs (1.0–4.8 k/mm^3)	0.9
RDW (0–14.7 units)	13.4	Monocyte Abs (0.1–0.8 k/mm^3)	0.6
MPV (6.8–10 um^3)	8.3	Eosinophil Abs (0–0.5 k/mm^3)	0
Platelet (130–400 k/mm^3)	271	Basophils Abs (0–0.2 k/mm^3)	0

Table 13.6 Chemistry

Sodium (135–145 mEq/L)	144	Albumin (3.4–4.8 g/dL)	2.3
Potassium (3.3–5 mEq/L)	3.9	Calcium (8.6–10.5 mg/dL)	8.4
Chloride (95–110 mEq/L)	106	Magnesium (1.5–2.6 mg/dL)	1.9
CO2 (24–32 mEq/L)	28	Phosphorous (2.4–5 mg/dL)	6.6
BUN (8–22 mg/dL)	32	LDH (90–200 U/L)	197
Creatinine (0.44–1.27 mg/dL)	3.9	BNP (0–100 pg/mL)	54
Glucose (70–110 mg/dL)	106		

Table 13.7 Urinalysis

Color	Yellow	Urobilinogen	Negative
Clarity	Clear	Nitrite	Negative
pH (4.8–7.8)	6.0	Leukocyte Est.	Negative
Specific gravity (1.002–1.030)	1.020	Bacteria/HPF	Few
Occult blood	3+	WBC (0–3/HPF)	3–5
Bilirubin	Negative	RBC (0–6/HPF)	50–100
Ketones	Negative	Cellular casts	1–2
Glucose	Negative	RBC casts	0
Protein	3+	Granular casts	3–5
Sulfosal	Negative	Hyaline casts	1–2

necrotizing, with some organisms such as *Staphylococcus aureus* and *Klebsiella pneumoniae* being infamous. Fungal infections, for example, invasive aspergillosis or pulmonary mucormycosis, typically in the setting of an immunodeficiency, can cause necrotizing pneumonia and hemoptysis. Atypical mycobacteria can cause cavitary disease and hemoptysis. Hospitalization within the previous 3 months increases the risk for nosocomial organisms, particularly methicillin-resistant *Staphylococcus aureus* and Gram-negative bacteria. Right-sided endocarditis and septic emboli can manifest in a variety of clinical presentations. IgA nephropathy is an immune-complex deposition disease that is often concomitant with infection and could explain the renal failure. Her initial presentation, however, is without fever or leukocytosis. Her history is not supportive of an infectious prodrome to a great

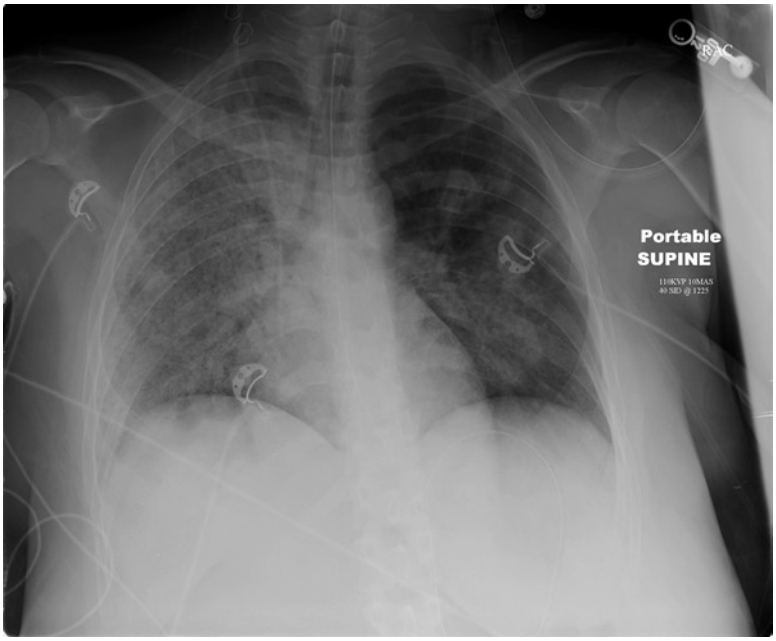

Fig. 13.3 Case 2 Chest X-ray

degree, lacking constitutional symptoms that would be expected with 2 weeks of illness. She does not have any history of recurrent skin infections, pneumonias, or sinus infections that could point to an underlying immunodeficiency.

The chest X-ray appearance is compatible with DAH, but can be easily mistaken for pulmonary edema or an infectious pneumonia. Hemoptysis is not always present even with alveolar hemorrhage. An unexplained radiographic infiltrate with acute anemia alerts to this possibility.

Hematuria is not expected with ATN and is more suggestive of glomerulonephritis, despite the lack of pathognomonic red-cell casts in the urine. The combination of glomerulonephritis and DAH is known as the pulmonary-renal syndrome and it can occur with a small-vessel vasculitis. Table 13.8 lists some of the more common causes of the syndrome.

This patient has a history of asthma, which is nearly always present with CSS. An ANCA-associated vasculitis similar to WG and MPA, CSS is associated with renal failure, sinusitis, and pulmonary infiltrates. The disease is often distinguished by prominent peripheral eosinophilia and mononeuritis. Renal failure with CSS is less common than with the other ANCA-associated vasculitides (25% with CSS compared to about 70% in WG and MPA). Mononeuritis multiplex is more common, seen in greater than 50% of CSS cases, presenting as asymmetric sensory and motor peripheral neuropathy, for example, burning pain of at least two limbs and/or difficulty using arms or walking depending on which peripheral nerve is involved.

Table 13.8 Pulmonary renal syndromes

ANCA-positive, systemic vasculitis
Wegener granulomatosis
Microscopic polyangiitis
Churg–Strauss
ANCA-negative, systemic vasculitis
IgA nephropathy
Behçhet disease
Henoch–Schönlein purpura
Cryoglobulinemia
Anti-GBM antibodies, Goodpasture's syndrome
ANCA-positive, without systemic vasculitis
Idiopathic pulmonary-renal syndrome
ANCA-positive, drug-associated vasculitis
Propylthiouracil
Hydralazine
Allopurinol
Sulfasalazine
Penicillamine
Autoimmune diseases
SLE
Rheumatoid arthritis
Scleroderma
Polymyositis
Mixed collagen vascular disease
Thrombotic microangiopathy
Antiphospholipid syndrome
Thrombotic thrombocytopenic purpura
Infection
Malignancy

Adapted from Papiris et al. [3]

While many of the ANCA vasculitides are treated similarly, Goodpasture syndrome with Anti-GBM differs in that there may be a greater likelihood of renal recovery with early initiation of plasmapheresis empirically until the diagnosis is excluded.

Malignancy could explain the protean findings in this case although to present with extensive severe disease as this without more constitutional signs and symptoms makes cancer unlikely. Catastrophic antiphospholipid syndrome causes multiorgan dysfunction, but greater than half of the patients have a prior history of thromboembolic disease or recurrent fetal loss. Laboratory evaluation often shows thrombocytopenia, signs of disseminated intravascular coagulation, or hemolysis. LDH, total bilirubin, platelet count, and coagulation studies were within normal range in this case.

Table 13.9 Immunologic tests

Complement C3 (92–210 mg/dL)	144
Complement C4 (14–49 mg/dL)	32
Complement CH50	84
Anti-neutrophil cytoplasmic antibodies C	Negative
Anti-neutrophil cytoplasmic antibodies P	1:160
Myeloperoxidase antibody (0–19 AU/mL)	45
Serine protease 3 antibody (0–19 AU/mL)	0
Anti-nuclear antibody	Negative
Anti-glomerular basement membrane antibodies	Negative

Differential Diagnosis

1. Pulmonary-Renal syndrome (ANCA-associated vasculitides, Goodpasture, SLE)
2. Infection
   Necrotizing Pneumonia
   Endocarditis
3. Malignancy

Workup

The patient was started empirically on broad-spectrum antibiotics and an immunologic and infectious disease evaluation embarked upon. Immunologic tests with a primary interest in the ANCAs were ordered (Table 13.9). Blood and urine cultures were obtained, but remained negative. An echocardiogram was normal, without evidence of valvular disease or ventricular dysfunction. Chest CT scan showed moderate to severe patchy consolidation in the lungs, involving all lobes. No cavities, effusions, or lymphadenopathy were present. The presence of hematuria, acute renal failure, and concern for a pulmonary-renal vasculitis syndrome warranted a renal biopsy early in the patient's course. Biopsy results showed crescentic glomerulonephritis with a pauci-immune immunofluorescence pattern.

What Is Your Final Diagnosis and Why?

Pulmonary-Renal Syndrome, ANCA-Associated Vasculitis

Microscopic Polyangiits
Rapidly progressive glomerulonephritis

Our patient's clinical presentation of hemoptysis, anemia, and radiographic diffuse airspace disease is highly suggestive of DAH. History, laboratory, and culture results are not supportive of an infectious cause. Her brain-naturietic peptide was within

normal limits and her echocardiogram did not reveal vegetations or ventricular or valvular dysfunction to suggest cardiogenic pulmonary edema. Although alveolar hemorrhage was not bronchoscopically confirmed, it can be reasonably assumed this case represents DAH.

Immunologic evaluation is significant for a highly elevated MPO antibody and the presence of P-ANCAs. P-ANCA tests are sensitive, but are very nonspecific, being present in a number of diseases including MPA, CSS, rheumatoid arthritis, and Goodpasture syndrome. Her negative ANA and complement levels essentially rule out SLE. She has no signs and symptoms of rheumatoid arthritis. Antiglomerular basement membrane antibodies are negative, eliminating Goodpasture from the differential. Although she has a history of asthma, this patient has no eosinophilia, sinusitis, or mononeuritis to suggest CSS. Kidney biopsy demonstrating the pauci-immune pattern further narrows the differential, eliminating many immune-deposition diseases such as IgA, SLE, and Goodpasture syndrome. This pattern is highly associated with ANCA vasculitides and is further confirmation of our clinical diagnosis.

Discussion

Microscopic polyangiitis is an idiopathic, autoimmune small-vessel necrotizing vasculitis with diffuse systemic effects. The disease is strongly linked to the presence of perinuclear ANCAs and it is frequently classified as an ANCA-associated vasculitis, along with WG and CSS. Its original description in 1923 distinguished it as a form of polyarteritis nodosa (PAN) in microscopic form, affecting only the small blood vessels. Today, MPA is clearly a distinct disease separate from PAN.

The exact incidence of the disease has been difficult to define due to historical classification as a variation of PAN and also because of variability between populations of different ethnicities, but overall is rare with estimates between 1 to 24 cases per million persons. Reports vary on male to female predominance, but more consistently the mean age of onset is reported in the sixth and seventh decades of life, which made our case very singular. Though ANCA-associated vasculitides appear more common among persons of European ancestry, MPA is much more common than WG in non-European populations when they occur. In a study comparing the incidence of renal vasculitis in the United Kingdom (UK) and Japan, investigators found nearly 100% of cases in Japan were MPA compared to about 50% in the UK population [2, 8].

Renal involvement is characteristic of MPA with studies reporting 80–100% of cases having some degree of kidney injury, ranging from mild proteinuria and hematuria to nephrotic proteinuria or complete failure. Focal segmental necrotizing glomerulonephritis is seen on biopsy in all patients [9]. Immunofluorescence staining reveals the pauci-immune pattern and is fairly distinct to the ANCA-associated vasculitides and helps distinguish them from other causes of small-vessel vasculitis, which show immune complex or complement deposition within the glomeruli.

MPA's predilection to pulmonary capillaritis leading to DAH makes it a frequent cause of pulmonary-renal syndrome. Cough and dyspnea are early symptoms of DAH with hypoxia and respiratory failure often ensuing.

The diffuse nature of small vessel vasculitis in MPA results in a wide range of clinical signs and symptoms. Nonspecific constitutional symptoms of illness are common, including fevers, chills, myalgias, arthralgias, and weight loss. Onset of the disease may be insidious or severe. About 60% of patients have skin involvement, palpable purpura being among the most common among a number of other nonspecific dermatologic signs. Peripheral neurologic manifestations are not uncommon with mononeuritis or polyneuropathies seen most commonly. Gastrointestinal symptoms such as pain or hemorrhage are not infrequent, occurring in over half of cases. Ocular, cardiac, and hepatobiliary manifestations are described. Ear, nose, and throat involvement is considered more characteristic of WG, but some overlap may exist and distinction between these two entities is not always clinically straightforward [8, 9].

Given the fact that vasculitides can have overlapping clinical features and that there is no specific diagnostic test, diagnosing MPA can be challenging. The practitioner must rely on a combination of histologic, radiographic, and laboratory findings in conjunction with the clinical presentation. A detailed review of all medications and inhalation exposures is necessary. Treatment for ANCA-associated vasculitides entails prolonged use of immunosuppressive medications, making the search for undiagnosed infection mandatory. Collagen-vascular diseases should be excluded.

Basic laboratory testing may show nonspecific signs of inflammation, including leukocytosis, thrombocytosis, or elevated CRP and ESR. Elevated serum creatinine and abnormal urinalysis, demonstrating proteinuria, hematuria, or evidence of glomerulonephritis should alert concern for pulmonary-renal syndrome when the chest X-ray is abnormal. This syndrome is a major cause of morbidity and mortality regardless of the underlying vasculitis and mandates acute hospitalization. Bronchoscopy may confirm alveolar hemorrhage and help rule out pneumonia, but transbronchial lung biopsies are typically nondiagnostic. Skin biopsies of palpable purpura may show leukocytoclastic vasculitis.

ANCAs in the diagnosis of MPA are extremely useful, but other conditions such as infections, autoimmune diseases, and sarcoidosis have been associated with positive ANCAs. The P-ANCA pattern and anti-MPO antibodies together have a sensitivity of 50–75%, therefore a negative test does not exclude the diagnosis [9]. Specificity for both tests together is reported with too much variability to rely upon. Ultimately, the diagnosis of MPA is based on a constellation of findings and active exclusion of other key illnesses.

The treatment strategy for MPA is much the same as for WG. This is in part due to the significant overlap of features and combined data in clinical trials, but also due to the lack of trials determining specific treatment for MPA. Given that most cases of MPA present with acute renal failure and are likely to have glomerulonephritis at time of diagnosis, by definition most are graded as generalized disease or severe. Dual agent therapy with systemic corticosteroids and cyclophosphamide in the hospital intensive care unit is recommended. Like WG, therapy has a significant

impact on outcomes, but MPA has a higher overall mortality compared with WG (27.5% vs. 13%) [8]. In contrast to WG, the relapse rate is lower. Induction can be achieved with corticosteroids and pulse cyclophosphamide until remission. Both WG and MPA patients were enrolled in recent trials comparing rituximab with cyclophosphamide for induction and found rituximab to be noninferior, but not associated with less adverse events. Further investigation is ongoing [8, 9]. Once induction of remission is reached, maintenance therapy is then begun with azathioprine or methotrexate for at least a year. Both have equivalent efficacy and relapse rates [10]. As with WG, plasmapheresis is believed to improve renal function, but not overall mortality. Other therapies under investigation for ANCA vasculitides include antitumor necrosis factor antibodies, anti-TNF α receptor analogs, and IV IG with some promising results. Outpatient monitoring for relapse is warranted.

Clinical Pearls

1. The pulmonary vasculitides have a high mortality when left untreated and can progress rapidly to serious organ failure and death. Early diagnosis and treatment are imperative.
2. The mainstay of treatment for the pulmonary vasculitides is high-dose and long-duration immunosuppressive therapy. Thorough exclusion of infection, malignancy, and other diseases that may present similarly is essential.
3. The ANCA tests are a useful tool when there is high clinical suspicion for the ANCA associated vasculitides; however many other nonvasculitic diseases and medications are associated with elevated ANCAs.
4. Open lung biopsy is usually necessary for the diagnosis of pulmonary WG as transbronchial lung biopsy and biopsies from other affected organs are of low diagnostic yield.

Questions

1. A 75-year-old man is referred for further evaluation of a chronic cough. He has a history of type 2 diabetes mellitus for the last 10 years and seasonal allergies with asthma. He is a lifetime nonsmoker. His chest X-ray shows a right upper lobe cavitary area with surrounding hazy infiltrates which are irregular. On review of systems, he endorses some mild weight loss and some hemoptysis but denies fevers or chills. Chemistry and CBC are only significant for mild normocytic anemia. His rheumatoid factor, ANA, and serum cryptococcal antigen are negative. Tests for cocci and blastomycosis are negative. A PPD was placed and is nonreactive. His P-ANCA is negative; however, his C-ANCA is 1:80. Based on these results, you determine the following:

   (a) The patient has limited stage WG; therapy with corticosteroids or methotrexate should be started

(b) The patient has early, generalized WG; therapy with corticosteroids and either cyclophosphamide or methotrexate should be initiated
(c) The lack of renal involvement at this point precludes the start of therapy
(d) Data is insufficient to recommend treatment at this time

2. A 45-year-old woman presenting with multiple cavitary lung nodules and renal failure is suspected of having WG. Her C-ANCA is 1:160 and her Serine Protease 3 Antibody level is 820. Other tests including an ANA, P-ANCA, and MPO Antibody test, are negative. Renal biopsy results are read as pauci-immune glomerulonephritis. She was hospitalized 1 month ago for pneumonia, which was treated with antibiotics, and she has been well since then. Blood and urine cultures are negative during this admission. The next step in the management of her disease is:

(a) Thoracic surgery evaluation for lung biopsy
(b) Bronchoscopy with transbronchial biopsies and bronchoalveolar lavage
(c) Initiation of therapy with cyclophosphamide and methylprednisolone
(d) Await results of serum quantiferon test and sputum acid-fast stains

3. The results of the lung biopsy specimen from the patient in question 2 reveal necrotic granulomas and evidence of vasculitis. It is classified as active, generalized disease and is treated with a combination of cyclophosphamide and corticosteroid induction therapy. Her renal function has returned to normal and her chest X-ray shows only minimal evidence of previous disease. During her third month on therapy, she presents to the hospital with 3 days of shortness of breath and a mild cough. On your evaluation, she is notably tachypneic and hypoxic, with room air oxygen saturations of 85%. She denies any hemoptysis.

Laboratory testing reveals a WBC count of 11k and a normal HCT. Her renal function is normal. Her chest X-ray reveals bilateral perihilar hazy infiltrates. Examination reveals normal breath sounds in all lung fields and her heart examination is normal. She has no cyanosis or peripheral edema. Her skin is warm to touch. She is admitted to the hospital under your care. You initiate the following:

(a) Plasma exchange therapy and start of rituximab for refractory disease
(b) Start of antibiotic therapy and supportive care
(c) Perform bronchoscopy to evaluate for diffuse alveolar hemorrhage
(d) Perform stat echocardiogram and start of therapy for congestive heart failure

4. All of the following are associated with a pauci-immune immunofluorescence pattern on renal biopsies except:

(a) Wegener granulomatosis
(b) Microscopic polyangiitis
(c) Anti-glomerular basement membrane antibodies (Goodpasture's)
(d) Churg–Strauss

5. A 60-year-old man is evaluated for a 6-month history of recurrent epistaxis and is found to have few ulcerative, friable lesions in his nasal cavities. A biopsy of an ulceration reveals granuloma formation. He denies any respiratory symptoms, skin rashes, joint pains, and has no hematuria. He denies fevers, chills, or weight loss. Laboratory evaluation reveals a normal creatinine and his C-ANCA is positive at 1:160 and his PR3 antibodies are positive at 550. You advise him that his findings are consistent with the diagnosis of WG and your recommendation is:

   (a) Start azathioprine or methotrexate given these have equal efficacy as induction therapy
   (b) Maintain observation of symptoms and frequent clinical follow-up, with start of cyclophosphamide and corticosteroids if renal or pulmonary involvement occurs
   (c) Start methotrexate and corticosteroids to prevent the development of further organ dysfunction
   (d) No further therapy is advised as the risk of progression at this stage is minimal

6. A 25-year-old woman with a 10-year history of SLE is admitted to the hospital with onset of cough, fevers, and diffuse arthralgias 3 days prior. Cough is notable for small amount of yellow phlegm mixed with frank blood. She has no rashes and denies abdominal pain, dysuria, or diarrhea. Medications include hydroxychloroquine and prednisone.

   Vital signs are normal and oxygen saturation is 95% on room air. Examination is significant for bilateral inspiratory crackles in the mid-lung fields. Heart exam is normal. Laboratory results reveal a WBC count of 12k, and a hematocrit of 25%, which is decreased from 30% previously. ANA is 1:320 and C3/C4 complement levels are within normal limits. Chest X-ray shows bilateral hilar airspace opacities. The patient is started on broad spectrum antibiotics with vancomycin, cefepime, and azithromycin. Bronchoscopy is performed with serial bronchoalveolar lavage (BAL) samples done in three different lobes. No endobronchial lesions or obvious source of blood is visualized. The BAL samples reveal PMN predominant cell counts and RBC counts between 3,000 and 4,000 cells in all of the samples. The next step in management of this patient's disease is:

   (a) Start of high-dose corticosteroids
   (b) Await results of BAL cultures
   (c) Begin plasma exchange therapy
   (d) Transfusion of packed red blood cells to maintain HCT > 30%

7. A 25-year-old woman presents for evaluation of an abnormal chest X-ray demonstrating bilateral hilar adenopathy. On review of systems she endorses low-grade fevers nightly and diffuse arthralgias. She has been previously healthy except for Graves disease being treated with propylthiouracil for the last 3 years.

Head and neck exams are normal. There are no oral lesions and no cervical or axillary lymphadenopathy is noted. Her lung and heart examinations are normal. Joints are unremarkable and there is no clubbing present. There is a tender, erythematous, nodular rash on both of her lower extremities.

Laboratory evaluation is significant for a normal CBC and chemistry. Urinalysis is normal. ANA is positive at 1:40. Complement C3/C4 and ACE levels are normal. ANCA-C and PR3 are negative while ANCA-P is positive at 1:160 and MPO is positive at 65. Rheumatoid factor is positive at 40. A lymph-node biopsy is planned, but you suspect:

(a) Rheumatoid arthritis is likely
(b) Positive antibody testing and exam are consistent with an ANCA-vasculitis
(c) Propylthiouracil should be discontinued due to a likely drug reaction
(d) Sarcoidosis is suggested and lung biopsies are indicated

8. Plasma exchange therapy should be considered in which of the following scenarios:

(a) Wegener Granulomatosis with rapidly progressive glomerulonephritis
(b) MPA with diffuse alveolar hemorrhage
(c) Anti-GBM antibody disease, Goodpasture syndrome
(d) All of the above

9. A 42-year-old woman is referred for evaluation of severe persistent asthma. A recent episode of wheezing led to an emergency room visit where a CBC was notable for a slightly elevated WBC count at 11.6k and a differential showing 12% eosinophils. A chest X-ray demonstrated hazy upper lobe opacities. She was diagnosed with early bronchopneumonia exacerbation of asthma and discharged with a course of prednisone and azithromycin.

On review of systems, she reports recurrent episodes of sinusitis and rhinitis for the last few years. A repeat CXR is clear of previously seen infiltrates. Which of the following is least likely the cause of her disease:

(a) Allergic bronchopulmonary aspergillosis
(b) Asthma
(c) Parasitic lung infection
(d) Churg–Strauss
(e) Chronic Eosinophilic Pneumonia

10. Necrotizing granulomas may be seen on pathologic biopsy specimens in all of the following, except:

(a) Wegener granulomatosis
(b) Microscopic polyangiitis
(c) Sarcoidosis
(d) Drug-induced lung toxicity
(e) Churg–Strauss

Answer

1. (d) Although this patient's results todate do not indicate an infectious cause of his lung cavity and he has a positive C-ANCA test, further evaluation is needed. The high sensitivity and specificity of the C-ANCA test is reliant on the pretest probability. This patient could have an ANCA-related vasculitis; however, without other clinical signs and symptoms the pretest probability is low at this point. Bacterial and fungal infections including invasive aspergillosis and mycobacterium tuberculosis, both of which should be considered in this patient, can be associated with a positive C-ANCA. A negative PPD should not exclude further workup for active pulmonary tuberculosis in the proper clinical scenario.
2. (a) This patient has a clinical signs compatible with WG and the positive C-ANCA and PR3 antibodies together in the setting of a high-pretest probability make it the likely diagnosis. However, because of the many diseases with similar presentations and the intense immunosuppressive therapy that is indicated for treatment of WG, a pathologic diagnosis is nearly always required in all but the most classic of cases.

   Bronchoscopy may be useful at the discretion of the clinician to exclude other causes of cavitary lung disease and to narrow the differential, but yield of transbronchial biopsy in diagnosing WG is extremely low.

   Initiation of therapy at this point is ill advised given this patient's recent history of pneumonia. Further exclusion of bacterial and fungal infections beyond simple blood, sputum, and urine cultures is indicated. The quantiferon test detects previous exposure to mycobacterium tuberculosis, but would not exclude active forms of infection.
3. (b) This patient's somewhat acute hypoxia, development of a radiographic infiltrate, and tachypnea generates a wide differential. Development of diffuse alveolar hemorrhage should be considered strongly; however, its occurrence in WG is somewhat less common than with other pulmonary vasculitides. Additionally, her normal HCT suggests there has not been significant blood loss to account for her hypoxia or the infiltrate. Bronchoscopy could be used to evaluate this further if her respiratory stability permitted, but this is less likely. Cardiac toxicity is a known potential side effect of cyclophosphamide therapy and should be entertained in the differential. An echocardiogram may help clarify this further but based on the patient's examination she has no clear signs of left or right ventricular failure. Her immunosuppressive regimen puts her at significant risk for development of infections, specifically pneumocystis jiroveci (formerly pneumocystis carinii) pneumonia which she has. Prophylaxis with trimethoprim-sulfamethoxazole or the like is recommended during immunosuppressive therapies such as hers and was not initiated in this case. While all of the above answers may have a role in her care, early initiation of antibiotic therapy is the best answer based on the likelihood of this presentation being infection.
4. (c) All of the above are associated with rapidly progressive glomerulonephritis, as are a number of other conditions such as SLE, IgA nephropathy, and

post-streptococcal glomerulonephritis. Only the ANCA-associated vasculitides (answers a, b, and d), as well as idiopathic forms, are associated with the pauci-immune pattern. Though presence of ANCAs and Anti-GBM antibodies characterize their respective diseases, both can be present at the same time. Therefore, determination of the renal glomerular immunofluorescence pattern helps distinguish these further.

5. (a) This patient can be classified as having limited WG given his symptoms are upper airway alone and given his lack of constitutional symptoms and renal involvement. His risk of progression to more severe stages of disease warrants start of medical therapy. Azathioprine, methotrexate, or corticosteroids alone have been used as induction therapy at this stage. If constitutional symptoms were present in this patient, he would be classified as early, generalized rather than limited and the recommended therapy would be corticosteroids in addition to either methotrexate or cyclophosphamide.
6. (b) The primary concerns with this patient's presentation are for infection, considering the history of SLE and current use of immunosuppressive medication, or for flare of SLE with a pneumonitis. Making the correct diagnosis in this patient is imperative as the treatment for her autoimmune disease would entail increasing the level of immunosuppression and to do this in the setting of an infection could be detrimental. Fever, cough, and leukocytosis are nonspecific and may be seen with infection or autoimmune pneumonitis, but the normal complement levels argue against an acute lupus flare. The chest X-ray findings along with the decrease in the HCT raise concern for diffuse alveolar hemorrhage which, if present, would argue for an acute lupus flare rather than infectious pneumonia. BAL results demonstrate the presence of red blood cells in the alveolar fluid, but do not reveal diffuse alveolar hemorrhage. Diagnosis is made when serial lavage specimens show increasing numbers of RBCs, occurring in multiple lobes of lung. Transfusion is not indicated at this time. The most likely cause is therefore infection, and continuing broad empiric antibiotic coverage while awaiting the results of the cultures is advisable.
7. (d) The patient is presenting with the classic signs and symptoms of a sarcoidosis variant known as Lofgren's syndrome. The syndrome is represented by the combination of hilar lymphadenopathy, fevers, arthralgias often predominant in the ankles, and the tender nodular rash of erythema nodosum. Symptoms can be somewhat acute prompting patients to present within days of onset. About 80% of patients will have resolution of symptoms within 2 years of onset.Rheumatoid arthritis may be distinguished by erosive joint disease and hilar lymphadenopathy is not a classic sign. RF tests are sensitive but nonspecific, so care must be used when ordering the test. Though ANCA-vasculitides can be associated with constitutional symptoms, this patient has no clear evidence otherwise of a vasculitis. Propylthiouracil has been associated with development of small-vessel vasculitis but again, the clinical scenario makes the diagnosis unlikely. About 20% of patients taking PTU have show ANCA positivity from simply using the medication alone and this does not represent a reaction warranting discontinuation of the drug.

8. (d) Plasma exchange is indicated for removal of circulating anti-GBM antibodies with Goodpasture syndrome. Evidence exists for improvement in renal failure in patients with WG and MPA although long-term outcome improvement has not been shown. Data is lacking to confirm the benefit of plasma exchange in patients with ANCA-vasculitides and DAH but based on outcomes in Goodpasture disease and smaller case series it should be considered.
9. (e) All of the diseases listed can be associated with the finding of peripheral eosinophilia and an asthma syndrome. However, chronic eosinophilic pneumonia (CEP) is unlikely to be associated with extra-pulmonary manifestations such as sinus involvement. Although rare reports of CEP with a normal chest X-ray exist, the disease generally has distinct, nontransient radiographic infiltrates.

   This patient meets the American College of Rheumatology criteria for the diagnosis of Churg–Strauss syndrome. Four of six criteria are required: asthma, eosinophilia >10%, mononeuropathy, transient chest X-ray infiltrates, paranasal abnormalities, and evidence of eosinophilic vasculitis on biopsy. The fact that many other diseases remain in the differential illustrates the diligence required to make a confident diagnosis of CSS.

   An IgE level, ANCAs, and stool ova and parasite examinations should be ordered. A low IgE level would make ABPA unlikely. Parasitic lung infection may require repeated stool testing and/or bronchoscopic evaluation. True asthma would be the diagnosis of exclusion should no other causes be found.
10. (b) All of the diseases listed may show evidence of granulomas on biopsy specimens except for microscopic polyangiitis. Although its clinical features and presentation can overlap significantly with WG and Churg–Strauss, only small-vessel vasculitis and mixed inflammatory infiltrate are seen.

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Part VI
Diffuse Parenchymal Lung Diseases

Chapter 14
Diffuse Parenchymal Lung Diseases

Livia Bratis and Thomas F. Morley

Abstract Diffuse parenchymal lung diseases (DPLD) encompass a wide variety of disorders. They share many features including clinical presentation, radiographic appearance, physiologic features, and even histological findings. Thus, identifying a specific cause is challenging. The diagnosis can be made in many patients based on history, physical examination, and noninvasive testing. However, transbronchial, thoracoscopic, or open lung biopsy may be required for definitive diagnosis.

Keywords Diffuse parenchymal lung disease • Interstitial lung disease • High-resolution computed tomography • Bronchoalveolar lavage • Pulmonary fibrosis • Restrictive ventilator defect • Nonproductive cough • Subpleural and basilar predilection • Prostanoid

Case 1

A 36-year-old Puerto Rican female presented after 10 days of persistent pain and swelling in the fourth digit of her left hand. She was given 7 days of antibiotics for presumed cellulitis with no response, so she presented to the emergency department for further evaluation and treatment. She denied any trauma to the finger, fever, or chills. Associated symptoms included a 10 lb weight loss over the past 6 months, and flat, hyper-pigmented skin lesions on her head and neck. She denied any shortness of breath, cough, palpitations, or abdominal symptoms.

Her past medical history was significant only for ovarian cyst. Surgical history was negative. Social history was negative for tobacco, alcohol, and illicit drug use.

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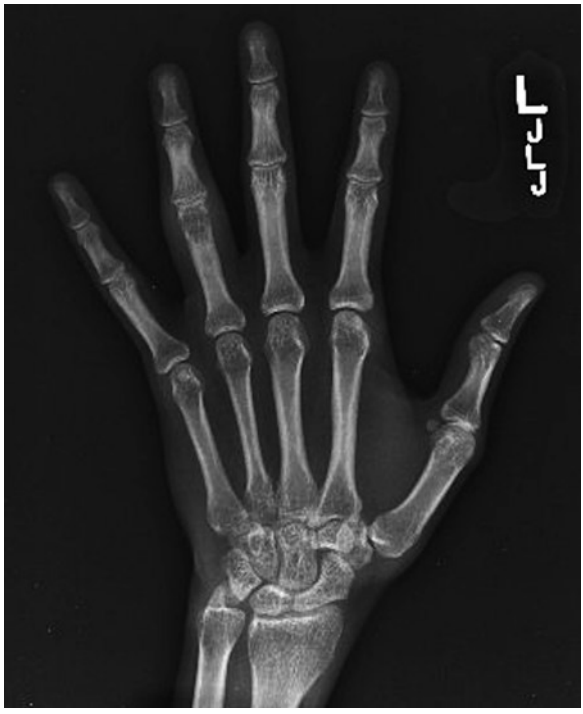

Fig. 14.1 This radiograph of the left hand showed significant erosion of the distal portion of the proximal phalanx of the fourth digit and associated soft tissue swelling

The patient worked as a consultant for an insurance company with no occupational exposures or exposure to tuberculosis. Family history was significant for diabetes. The patient was not on any outpatient medications aside from a recent course of cephalexin. She had no known drug allergies.

Physical examination was remarkable. Vital signs showed temperature 98.6°F, blood pressure 100/63 mmHg, heart rate 94/min, respiratory rate 18/min, and oxygen saturation 97% on room air. She was awake, alert, oriented, and in no distress. HEENT exam revealed multiple, papular, hyper-pigmented areas on her forehead, and several small nodular lesions on her scalp. Neck was supple without jugular venous distention or thyromegaly. Heart rate and rhythm were normal without murmur, rub, or gallop. Lungs were clear to auscultation. Abdomen was soft, nontender, nondistended, and without organomegaly. Examination of her left hand revealed swelling, pain, and erythema of the fourth digit, especially the proximal phalanx. Lymphatic and neurologic exams were normal.

Further evaluation provided the following information. EKG showed normal sinus rhythm. Left hand x-ray revealed osseous lucencies in the fourth proximal phalanx with cortical thinning and overlying soft tissue swelling (Fig. 14.1). Chest x-ray showed bilateral interstitial nodules in the mid lung fields with hilar adenopathy (Fig. 14.2). CT chest, abdomen, and pelvis further delineated bilateral interstitial nodules, hilar adenopathy, and nodules in her liver and spleen (Figs. 14.3 and 14.4).

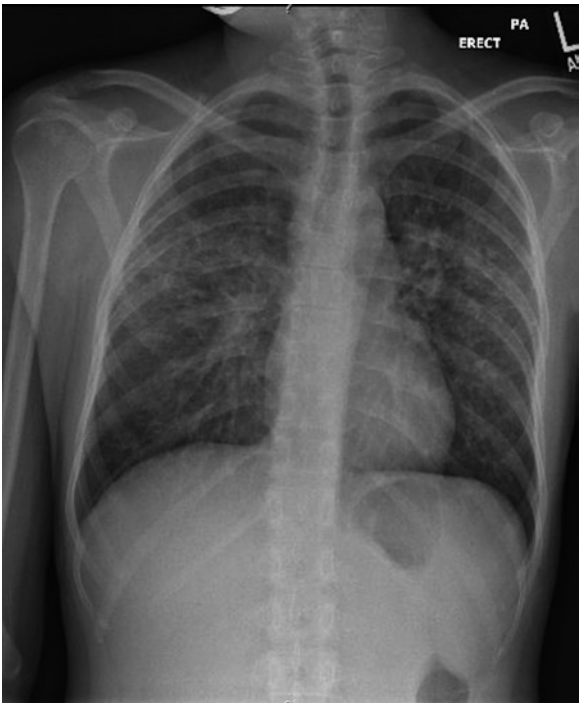

Fig. 14.2 The PA chest radiograph demonstrated bilateral, hilar adenopathy and bilateral, upper lobe interstitial infiltrates

Laboratory analysis was unimpressive. Arterial blood gas showed pH 7.48 (7.35–7.45), $PaCO_2$ 39 mmHg (35–45 mmHg), PaO_2 92 mmHg (80–95 mmHg), HCO_3^- 29 mEq/L (22–26 mEq/L), and saturation of 98% (95–100%) on room air. Serum electrolytes and complete blood count were normal. C-reactive protein was 1 mg/dL (0–1.0 mg/dL).

With the Presented Data What Is Your Working Diagnosis?

Sarcoidosis, scleroderma, dermatomyositis, or metastatic cancer

Workup

At this point, either a bone biopsy, skin biopsy, or transbronchial lung biopsy was considered to make a definitive diagnosis. The patient was reluctant to undergo skin biopsy of her facial lesions. Therefore, transbronchial lung biopsy was obtained. Pathology demonstrated noncaseating granulomas. Cultures and stains were negative for acid fast bacilli and fungal forms.

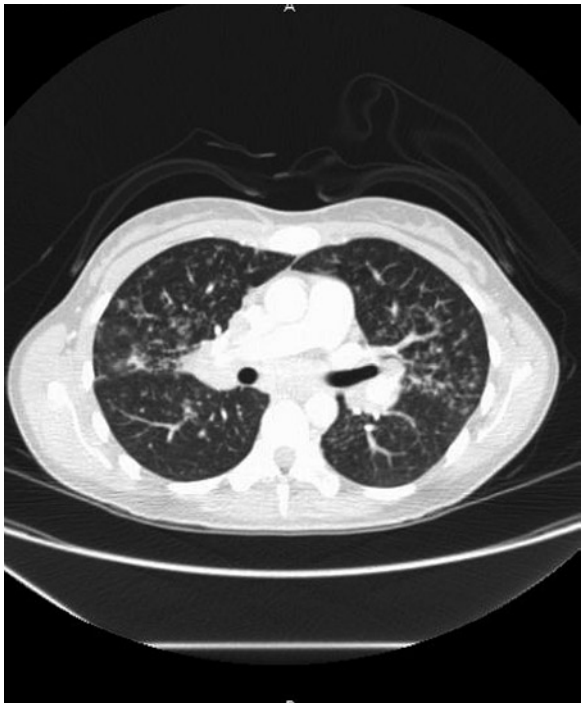

Fig. 14.3 Chest CT with contrast at the level of the bronchus intermedius revealed bilateral, upper lobe reticulonodular infiltrates, and hilar adenopathy

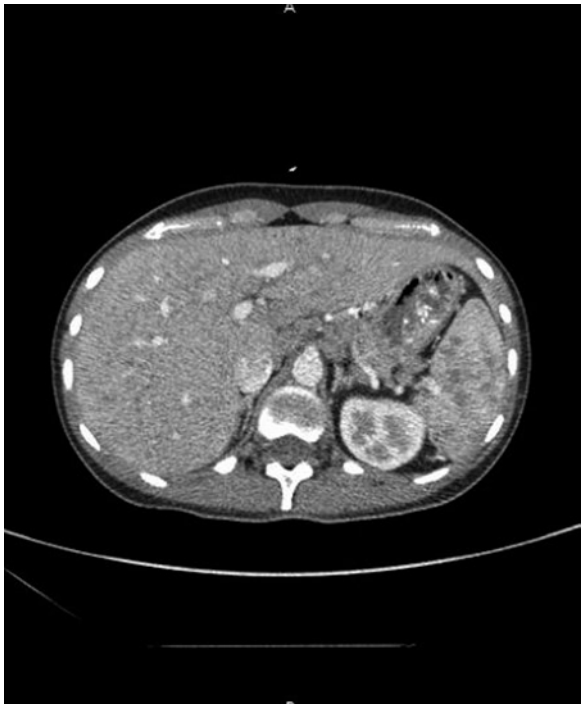

Fig. 14.4 CT of the abdomen with contrast demonstrated hepatomegaly and a mottled appearing spleen

What Is Your Diagnosis and Why?

The diagnosis is sarcoidosis. The differential diagnosis for bilateral interstitial nodules is extensive and includes occupational diseases, infections, collagen vascular diseases, inhalation injury, carcinoma, and idiopathic lung disease. This patient's history and lab work excluded occupational, inhalation, and infectious causes. When lung infiltrates are combined with joint swelling, it narrows the differential. However, the aspect of this case that makes the diagnosis is the presence of hilar adenopathy. In the absence of infection, the combination of nodular interstitial disease and adenopathy strongly suggests the diagnosis of sarcoidosis or carcinoma. Transbronchial lung biopsy revealed the diagnosis. Fortunately, this test has a high diagnostic yield for sarcoidosis and carcinoma, which were the top two on the differential. Pathology revealed noncaseating granulomas indicative of sarcoidosis.

Sarcoidosis is an idiopathic disease resulting in diffuse noncaseating granulomas, most commonly in the lung, eyes, or skin. It is a multisystem disease also affecting the conduction system, lymphatic system, brain, liver, spleen, and bone. It is generally responsive to immune modulators, most specifically corticosteroids. This patient had a reasonable response to corticosteroids at a starting dose of 1 mg/kg of prednisone, with resolution of the bone lesion, and improvement of pain and swelling. However, the skin lesions and chest radiographic findings did not improve. At the fifth week of therapy, methotrexate 15 mg weekly was added to her regimen. Within 4 weeks, the patient's skin lesions underwent significant improvement. Slow radiographic improvement in her chest x-ray was noted. She continued to improve on therapy.

Case 2

A 50-year-old African American female presented to the emergency department with complaints of progressive shortness of breath and cough productive of yellow sputum of 3 months' duration. She admitted to more indolent symptoms of dyspnea and fatigue for about 1 year prior to presentation. Initially, she was treated with empiric corticosteroids with little to no response. Her symptoms were persistent with occasional wheezing and intermittent chest pain. She denied associated fever or weight loss.

Her past medical history was significant for systemic lupus erythematous, hypertension, degenerative joint disease, brain aneurysm, anxiety, depression, uterine fibroids, and ileitis. Past surgical history was notable for endovascular coiling for her brain aneurysm, tubal ligation, and neck mass excision. Social history was negative for alcohol and illicit drug use. She admitted to smoking one pack of cigarettes per day for 30 years. She worked as an office clerk. Family history was significant for brain and lung cancer, as well as brain aneurysms in her immediate family.

Her outpatient medications included prednisone 20 mg daily, albuterol inhaler as needed, amlodipine/valsartan/hydrochlorothiazide 5/160 mg daily, hydrocodone/

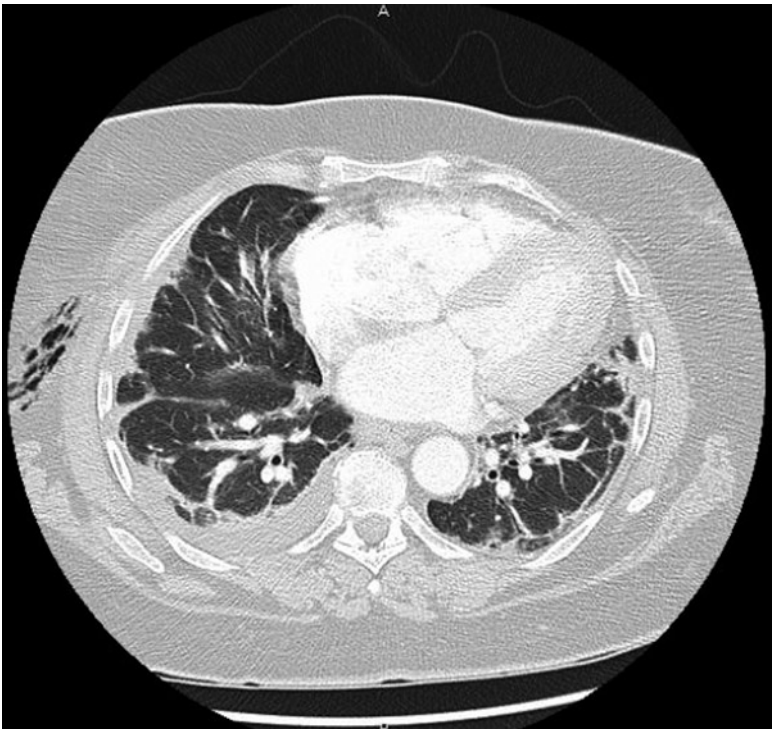

Fig. 14.5 Chest CT with contrast at the level of the left atrium showed subpleural infiltrates bilaterally. Thickening of the interlobular septae and areas of traction bronchiectasis were present. There was a small right pleural effusion. A small area of subcutaneous emphysema was noted in the right chest wall at the site of a prior chest tube

acetaminophen 7.5/500 mg every 6 h as needed, and inhaled fluticasone/salmeterol 250/50 mcg one puff twice daily.

Physical examination was as follows. Vital signs showed temperature 97.5°F, blood pressure 120/58 mmHg, heart rate 74/min, respiratory rate 18/min, and oxygen saturation 98% on 2 L/min of oxygen. The patient was awake, alert, oriented, and in no distress. HEENT exam was negative. Neck was without jugular venous distention or thyromegaly. Heart rate and rhythm were normal without murmur, rub, or gallop. Lung exam revealed bibasilar crackles and expiratory wheeze. The abdominal exam was benign. Her right upper extremity had multiple areas of hyperpigmented patches. Neurologic exam was normal.

Further evaluation revealed the following data. EKG showed sinus bradycardia. Chest x-ray showed diffuse interstitial pattern and volume loss on the right. Chest CT delineated patchy ground glass infiltrates with peripheral, subpleural infiltrates, and mild basilar fibrotic changes (Fig. 14.5).

Laboratory analysis was unimpressive. Serum electrolytes were normal. Calcium was normal. Complete blood count was normal except for hemoglobin of 10 gm/dL (12.1–15.1 gm/dL).

With the Presented Data What Is Your Working Diagnosis?

The working diagnosis is usual interstitial pneumonitis or nonspecific interstitial pneumonitis. However, sarcoidosis, desquamative interstitial pneumonitis, pneumoconiosis, and hypersensitivity pneumonitis need to be excluded.

Workup

At this point, a lung biopsy was required for diagnosis. The patient underwent video-assisted thoracoscopic lung biopsy. Multiple lung biopsies were taken. Pathology showed areas of diffuse parenchymal lung disease with interstitial fibrosis and honeycombing. Temporal heterogeneity and fibroblastic foci were also identified.

What Is Your Diagnosis and Why?

The diagnosis is usual interstitial pneumonitis. The differential diagnosis for an indolent presentation of an interstitial lung disease is substantial including occupational, drug induced, collagen vascular disease, and inhalation injury by way of hypersensitivity reaction, or idiopathic pulmonary fibrosis. The patient's medical and social history rule out the diagnosis of drug induced or occupational lung disease. The patient denied any inhalation injury and showed no systemic signs of collagen vascular disease. The radiographic pattern of temporal heterogeneity, peripheral honeycombing, and basilar predilection suggests the diagnosis of usual interstitial pneumonitis. Pathology confirmed the diagnosis.

Usual interstitial pneumonitis is a devastating idiopathic fibrotic process that typically presents in the fifth or sixth decade of life. Common symptoms are dyspnea on exertion and dry cough. It progresses toward end stage lung disease within 2–5 years with little or no chance of cure. It is defined by its lack of response to immune modulators such as corticosteroids. The only definitive cure is lung transplantation.

Discussion

Historically, diffuse interstitial lung disease was a term used to describe a heterogeneous group of pulmonary disorders that shared certain clinical, radiographic, physiologic, and pathologic characteristics. In general, these diseases, thought to be confined to the lung interstitium, are associated with lung fibrosis and cause a restrictive ventilatory defect. However, it has become clear that many of these disorders are not confined to the interstitium, and may involve alveolar and vascular structures. Also, some diffuse lung diseases are not associated with lung fibrosis or

restriction. For these reasons, some authors have advocated that these disorders be reclassified as diffuse parenchymal lung diseases (DPLD) [1]. This classification has the advantage in that it is more inclusive incorporating alveolar filling diseases (e.g., eosinophilic pneumonia, alveolar proteinosis, and alveolar hemorrhage). It also allows for inclusion of disorders associated with normal lung volume (e.g., pulmonary Langerhans cell histiocytosis), and increased lung volume (e.g., lymphangioleiomyomatosis).

The remainder of this chapter will discuss the classification, characterization, and the diagnosis of diffuse parenchymal lung diseases.

Classification

DPLD are characterized by diffuse bilateral radiographic infiltrates. Exertional dyspnea and cough are invariably present. The cough is usually dry, but may be productive (e.g., bronchoalveolar cell carcinoma or infections), or associated with hemoptysis (e.g., cancer, infections, or alveolar hemorrhage). If pulmonary fibrosis or vascular obstruction is present, then exercise oxygen desaturation may be present. Pathologically, distortion of the airway, alveolar, or interstitial structures may be present. Finally, restriction may be present if pulmonary fibrosis is the primary pathology. However, lung volume may be normal or elevated in certain disorders.

DPLD may be divided into those with a known cause and those that are idiopathic (Table 14.1). In patients with known causes of DPLD, the diagnosis may be obvious.

Table 14.1 Causes of diffuse parenchymal lung diseases

Known causes	Idiopathic causes
Pneumoconioses	Sarcoidosis
Hypersensitivity pneumonitis	Idiopathic interstitial pneumonias IPF, AIP, DIP, NSIP, COP, LIP
Infections	Alveolar hemorrhage syndromes
Drug induced lung damage	Pulmonary infiltrates with eosinophilia
Radiation induced damage	Amyloidosis
DPLD associated with connective tissue disease	Lymphangioleiomyomatosis
DPLD associated with inflammatory bowel disease	Tuberous sclerosis
Malignancy	Neurofibromatosis
DPLD associated with vasculitis	Niemann–Pick disease
Chronic aspiration	Gaucher's disease
Anti-synthetase syndrome	Hermansky–Pudlak syndrome
	Ankylosing spondylitis
	Pulmonary veno-occlusive disease

IPF idiopathic pulmonary fibrosis, *AIP* acute interstitial pneumonitis, *DIP* desquamative interstitial pneumonitis, *NSIP* nonspecific interstitial pneumonitis, *COP* cryptogenic organizing pneumonia, *LIP* lymphocytic interstitial pneumonitis

Table 14.2 Drugs associated with diffuse parenchymal lung damage

Condition	Responsible agent
Organizing pneumonia	Amiodarone, bleomycin, cocaine, cyclophosphamide, methotrexate, minocycline, mitomycin-C, penicillamine, sulfasalazine, tetracycline
Hypersensitivity pneumonitis	Azathioprine plus 6-mercaptopurine, busulfan, fluoxetine, radiation
Interstitial pneumonia or Fibrosis	Amphotericin B, bleomycin, busulfan, carbamazepine, chlorambucil, cocaine, cyclophosphamide, diphenylhydantoin, flecainide, heroin, melphalan, methadone, methotrexate, methylphenidate, methylsergide, mineral oil aspiration, nitrofurantoin, nitrosoureas, procarbazine, silicone injection, tocainide, vinca alkaloids (with mitomycin)
Noncardiac pulmonary edema	Ritodrine, terbutaline, chlordiazepoxide, cocaine, cytarabine, ethiodized oil (IV and aspiration), gemcitabine, heroin, hydrochlorthiazide, methadone, mitomycin-C, phenothiazines, protamine, sulfasalazine, tocolytics, tricyclic antidepressants, tumor necrosis factor, vinca alkaloids (with mitomycin)
Parenchymal hemorrhage	Anticoagulants, azathioprine plus 6-mercaptopurine, cocaine, mineral oil aspiration, nitrofurantoin, radiation
Pulmonary infiltrates	Amiodarone, amphotericin B, bleomycin, carbamazepine, diphenylhydantoin, ethambutol, etoposide, granulocyte-macrophage colony-stimulating factor, isoniazid, methotrexate, minocycline, mitomycin-C, nitrofurantoin, para-aminosalicylic acid, procarbazine, radiation, sulfasalazine, sulfonamides, tetracycline, trazodone

If a patient had remote exposure to inhalation of an inorganic dust (e.g., asbestos, silica, coal) then pneumoconiosis may be diagnosed from the clinical and radiographic features. Likewise, known exposure to an organic antigen that can acutely or chronically damage the lung (e.g., hypersensitivity pneumonitis) can be identified by appropriate testing and avoidance can prevent progressive lung disease. Unfortunately, hypersensitivity pneumonitis is under recognized.

Infectious causes of DPLD in an immune competent host are usually readily identified. In the immunocompromised host, opportunistic pneumonias (e.g., *Pneumocystis jiroveci*) need to be identified.

A large number of medications have been shown to cause acute and/or chronic lung damage (Table 14.2) [2]. A complete review of all medications must be undertaken in patients with DPLD. Failure to consider a medication as a potential cause can result in severe, permanent lung damage.

Radiation injury to the lung is usually apparent. Acute injury (starting 1–3 months after completion of radiation) is usually associated with dry cough, dyspnea, and fever. It often improves with corticosteroid administration. Chronic injury occurs later and is not steroid responsive. In both acute and chronic radiation lung disease, injury is usually limited to the radiation portal and depends on the cumulative radiation dose [3].

Table 14.3 Extrathoracic manifestations of DPLD

System involved	Diagnosis
Nasal/Sinuses	Wegener's granulomatosis
Arthritis	Rheumatoid arthritis
	Sarcoidosis
	Connective tissue diseases
	Granulomatous vasculitis
	Sjogrens syndrome
Skin	Sarcoidosis
	Connective tissue diseases
	Granulomatous vasculitis
	Dermatomyositis
	Scleroderma
Central nervous system	Connective tissue diseases
	Sarcoidosis
	Lymphomatoid granulomatosis
Muscle	Sarcoidosis
	Polymyositis
	Dermatomyositis
	Anti-synthetase syndrome
Gastrointestinal	Scleroderma
	Polymyositis
	DPLD with inflammatory bowel disease
Renal	Wegener's granulomatosis
	Goodpasture's syndrome
	Connective tissue diseases
	Scleroderma

DPLD due to malignancy may take the form of diffuse alveolar infiltrates (e.g., lymphoma or bronchoalveolar cell carcinoma). With lymphangitic spread of cancer, the infiltrates are more frequently ground glass in appearance, and beading as well as thickening of the interlobular septae are noted. Pleural effusion can develop. With a known history of malignancy, the diagnosis is often suspected. However, when the diagnosis is in question pathology is required.

In DPLD associated with inflammatory bowel disease, collagen vascular disease, vasculitis, and some idiopathic disorders, respiratory symptoms may not be the primary complaints. In fact, extrapulmonary signs and symptoms may predominate and even aid in appropriate testing and diagnosis. The specific extrapulmonary systems involved with specific causes of DPLD are shown in Table 14.3.

Clinical Features

Patients with DPLD generally present in one of five ways: (1) pulmonary symptoms including dyspnea, chest pain, pleurisy, cough, or exercise desaturation; (2) extrapulmonary symptoms associated with DPLD; (3) abnormal chest radiograph and/or CT scan; (4) occupational exposure; or (5) abnormal pulmonary function tests.

The clinical features of specific DPLD vary with age, gender, rate of disease progression, and extrapulmonary (systemic) manifestations. A complete history and physical examination is fundamentally important for accurate diagnosis and treatment. Potential mediators of lung injury such as organic dusts (hypersensitivity pneumonitis), inorganic dusts (pneumoconiosis), and medications must be identified and eliminated. Although radiation damage to the lung may not be eliminated in all cases, dose limitation and avoidance of exacerbating medications (e.g., adriamycin) should mitigate injury.

Age at presentation can be helpful. Patients who present at an age less than 40 years will more frequently have sarcoidosis, connective tissue disease associated DPLD, lymphangioleiomyomatosis, pulmonary Langerhans cell histiocytosis, familial idiopathic pulmonary fibrosis (IPF), Gaucher's disease, or Hermansky–Pudlak syndrome. Patients with IPF, pneumoconiosis, or chronic aspiration are more frequently older than 50 years at the time of presentation.

Gender is rarely sufficient to narrow the differential diagnosis. However, lymphangioleiomyomatosis and pulmonary involvement with tuberous sclerosis occur exclusively in premenopausal females.

The duration of symptoms prior to presentation can be helpful in suggesting certain diagnoses. Acute or subacute presentation, over weeks to months, occurs with bronchiolitis obliterans organizing pneumonia (BOOP), acute eosinophilic pneumonia, connective tissue disease associated DPLD, and infectious pneumonias. IPF, silicosis, anthracosis, and asbestosis progress over years. For the pneumoconioses, DPLD requires more than 20 years after exposure to become clinically apparent. IPF progresses over 3–5 years. Sarcoidosis, hypersensitivity pneumonitis, as well as some drug induced and infectious diseases can have acute, subacute, or chronic progression.

Smoking history is important. Certain DLPD occur significantly more frequently in patients who are current or former smokers. These include pulmonary Langerhans cell histiocytosis, desquamative interstitial pneumonitis, respiratory bronchiolitis-interstitial lung disease, and IPF. In patients with Goodpasture's disease, active smoking is believed to aggravate pulmonary hemorrhage. The putative mechanism is that cigarette smoke causes further damage to the alveolar capillary membrane, which exposes more basement membrane anti-basement membrane antibody.

Family history is rarely useful. However, some DPLD clearly have a familial component. These include IPF, sarcoidosis, tuberous sclerosis, neurofibromatosis, Neiman–Pick disease, Gaucher's disease, and Hermansky–Pudlak syndrome.

Signs and Symptoms

Dyspnea on exertion is common with DPLD. The severity, duration, and progression of symptoms should be evaluated. Patients with severe dyspnea frequently reduce their activity to match disease severity. Because of this, they frequently underestimate and under report the severity of their symptoms. Alternatively, the patients may attribute their dyspnea to other causes such as obesity or deconditioning. Family members may be helpful in providing more reliable history in these circumstances.

Sudden worsening of dyspnea in a DPLD patient should engender a workup for pulmonary embolism and spontaneous pneumothorax. Spontaneous pneumothorax occurs with increased frequency in lymphangioleiomyomatosis, pulmonary Langerhans cell histiocytosis, tuberous sclerosis, and neurofibromatosis.

A dry, nonproductive cough is common. A productive cough is unusual. Occasional patients with bronchoalveolar cell carcinoma will expectorate mucoid sputum. Hemoptysis, when present, should lead to a workup for pulmonary hemorrhage syndrome, lymphangioleiomyomatosis, or malignant transformation as with IPF.

Chest pain is uncommon. However, pleuritic chest pain, when present, suggests lupus, rheumatoid disease, certain drug induced diseases (e.g., macrodantin, hydralazine), or spontaneous pneumothorax. Substernal discomfort is associated with sarcoidosis.

The physical examination of DPLD patients is usually nondiagnostic. Extrapulmonary findings (e.g., skin rash, arthritis, sclerodactyly, etc.) may on occasion suggest a specific diagnosis. The pulmonary examination is often normal, but may demonstrate bibasilar crackles. The cardiac examination is also usually normal unless pulmonary hypertension is present. In this setting, a prominent pulmonary component to the second heart sound is noted, and/or a right ventricular lift and gallop may be present. These may be prominent findings in progressive systemic sclerosis patients with pulmonary vascular involvement. Clubbing is a prominent finding in patients with IPF and asbestosis. It is uncommon in sarcoidosis, and DPLD associated with connective tissue diseases.

Diagnostic Evaluation

There are a large number of potential causes for DPLD. Therefore, it is necessary to perform a substantial number of baseline studies to determine a specific cause [4]. Laboratory studies include: biochemistry profile (for renal and liver function), complete blood count with differential, creatine kinase, urinanalysis, HIV testing, hypersensitivity precipitin panel, antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), rheumatoid factor, antitopoisomerase (antiScl70), and anti-JO-1 antibodies. Angiotensin converting enzyme, gammaglobulin levels, and C-reactive protein are often included in the workup, but these tests are largely nonspecific. If the ANA is positive, then antidouble stranded DNA and antiextractable nuclear antigen antibodies (anti-Sm and antiribonucleoprotein) are obtained to evaluate for systemic lupus erythematosis and mixed connective tissue disease. If pulmonary hemorrhage is suspected, then antiglomerular basement membrane antibodies, ANA, ANCA, antiphospholipid antibodies, and antistreptococcal antibodies are ordered.

Chest radiography generally reveals an “interstitial” pattern with a nodular, reticular, or mixed pattern being identified. Alveolar patterns can also be seen (e.g., alveolar hemorrhage, eosinophilic pneumonia, BOOP, or bronchoalveolar cell carcinoma). The severity of chest radiographic findings often does not correlate well with clinical severity. Comparison with prior chest radiographs is very helpful in determining disease progression. Chest radiographs may be normal in early disease

(e.g., hypersensitivity pneumonitis, pneumocystis juroveci). The distribution of disease within the lung is also helpful. Upper lobe distribution suggests sarcoidosis, pulmonary Langerhans cell histiocytosis, silicosis, anthracosis, ankylosing spondylitis, and the necrobiotic form of rheumatoid arthritis (RA). Lower lobe distribution is generally associated with RA with usual interstitial pneumonitis, IPF, and asbestosis. Prominent adenopathy is most often associated with sarcoidosis, malignancy, infection, and silicosis. Calcified pleural and/or diaphragmatic plaques suggest asbestos related disease.

High resolution computed tomography (HRCT) of the chest provides greater spatial resolution than chest radiographs or routine chest CT scanning. DPLD may be identified in patients with normal chest radiographs using HRCT. Several HRCT patterns can be helpful in narrowing the differential diagnosis [5, 6]. Subpleural reticular opacities with honeycombing and traction bronchiectasis are most frequently associated with IPF, asbestosis, and rheumatoid lung. Upper lobe cystic disease with nodular densities without volume loss suggests pulmonary Langerhans cell granulomatosis. Bilateral, upper lobe, reticular disease with bilateral hilar adenopathy suggests sarcoidosis or another granulomatous disease. Linear calcified pleural and/or diaphragmatic plaques are associated with asbestos related disease.

Gallium-67 lung scanning is no longer used in the routine evaluation of DPLD. The role of (18) F-2-deoxy-2-fluoro-D-glucose positron emission tomography (PET) in DPLD is not known. PET scanning is positive in patients with lymphangitic cancer. However, it may also be positive in benign diseases such as sarcoidosis or other granulomatous diseases, and pulmonary Langerhans cell granulomatosis.

Pulmonary function testing including spirometry, lung volume determination, and diffusing capacity determination should be obtained on all DPLD patients. Resting and exercise pulse oximetry should be evaluated. If possible, a baseline 6-min walk distance should be determined. Diffuse disease associated with pulmonary fibrosis generally results in a restrictive defect with a normal or increased FEV1/FVC ratio. However, DPLD may be associated with an obstructive pattern (e.g., a reduced FEV1/FVC ratio) such as seen with lymphangioleiomyomatosis, tuberous sclerosis, COPD and ILD, hypersensitivity pneumonitis, and sarcoidosis. Reduction in the diffusing capacity is a frequent but nonspecific finding. Severe reduction in the DLCO with relatively normal lung volumes suggests lymphangioleiomyomatosis, pulmonary Langerhans cell granulomatosis, or combined emphysema and ILD.

Fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) obtains samples of cells and fluid from the distal airways and alveolar structures. BAL tends to be most useful in patients with acute disease such as pulmonary hemorrhage, infections, malignancy, and eosinophilic causes [4, 7, 8]. In patients with alveolar hemorrhage, the BAL fluid usually demonstrates 30% or greater hemosiderin-laden macrophages. The presence of lipid-laden macrophages suggests a lipoid pneumonia. Langerhans cells suggest pulmonary Langerhans cell histiocytosis. BAL is less frequently diagnostic in patients with chronic DPLD such as IPF. BAL can be diagnostic in patients with pneumoconiosis, but it is rarely necessary because the history of specific occupational exposure and radiographic features are usually sufficient to make the diagnosis.

Lung biopsy is required to make a specific diagnosis when the previously described techniques, including biopsy of extrathoracic sites, prove inadequate [9, 10]. Transbronchial lung biopsy has a reasonably good yield in specific DPLD such as sarcoidosis, lymphangitic carcinomatosis, infection, BOOP, and Goodpasture's syndrome. Endobronchial biopsy is useful in sarcoidosis patients. However, many DPLD are associated with a heterogeneous, patchy distribution within the lungs and may be missed with transbronchial lung biopsy. In these patients, surgical lung biopsy is necessary by either thoracotomy or video assisted thoracoscopic surgery (VATS). Diagnostic accuracy is similar for both procedures. It is important to realize that patients with DPLD are of an advanced age with significant comorbidities. In patients with advanced honeycombing without lesser areas of involvement and patients with serious cardiovascular disease, surgical biopsy should not be undertaken. Therefore, it must be emphasized that the risk/benefit ratio of surgical lung biopsy versus conservative management must be weighed.

Lung biopsies are generally taken from areas of actively involved lung and areas of less involved or normal lung. Areas with advanced honeycombing rarely yield a specific diagnosis. The right middle lobe and lingula are best avoided as they often contain areas of nonspecific fibrosis.

Conclusion

Diffuse parenchymal lung disease, in general, implies inflammation and/or fibrosis of the alveolar walls resulting in profound effects on the capillary endothelium and epithelial lining. Interstitial fibrosis can occur after an insult that affects the permeability of the alveolar-capillary membrane causing serum contents to spill into the alveolar spaces. Fibroblastic proliferation and excessive collagen deposition occur as a direct result of injury or as a result of the lung's inflammatory reaction. Identifying the cause of diffuse parenchymal lung disease can be challenging. They share many features including clinical presentation, radiographic appearance, physiologic features, and even histological findings. A specific diagnosis can be made in many patients based on history, physical examination, and noninvasive testing. However, transbronchial, thoracoscopic, or open lung biopsy may be required for definitive diagnosis.

Questions

1. Patients that present with symptoms of DPLD at age less than 40 years are likely to be any of the following except:

   (a) Pulmonary Langerhans cell histiocytosis
   (b) Sarcoidosis
   (c) Lymphangioleiomyomatosis
   (d) Hermansky–Pudlak syndrome
   (e) Pneumoconiosis

2. Acute or subacute presentation over weeks to months excludes the diagnosis of:

   (a) Sarcoidosis
   (b) Idiopathic pulmonary fibrosis
   (c) Bronchiolitis obliterans organizing pneumonia
   (d) Acute eosinophilic pneumonia
   (e) Drug-induced pneumonitis

3. Which of the following does not have a familial component?

   (a) Tuberous sclerosis
   (b) Gaucher's disease
   (c) Idiopathic pulmonary fibrosis
   (d) Acute eosinophilic pneumonia
   (e) Sarcoidosis

4. An associated symptom of substernal chest pain with DPLD can be useful in diagnosing:

   (a) Idiopathic pulmonary fibrosis
   (b) Drug-induced pneumonitis
   (c) Acute eosinophilic pneumonia
   (d) Sarcoidosis
   (e) Alveolar proteinosis

5. Sarcoidosis is associated with all of the following, except:

   (a) Extrapulmonary manifestations
   (b) Lymphadenopathy
   (c) Clubbing
   (d) Diffuse parenchymal infiltrates
   (e) Familial component

6. Which of the following radiographic findings are consistent with idiopathic pulmonary fibrosis?

   (a) Ground glass infiltrates
   (b) Predominantly apical pattern
   (c) Hilar adenopathy and diffuse interstitial disease
   (d) Subpleural and basilar predilection
   (e) Homogeneous interstitial disease

7. Which of the following diseases is typically not corticosteroid responsive?

   (a) Sarcoidosis
   (b) Acute interstitial pneumonia
   (c) Idiopathic pulmonary fibrosis
   (d) Acute radiation lung injury
   (e) Bronchiolitis obliterans organizing pneumonia

8. Typical presentation for idiopathic pulmonary fibrosis is:

   (a) Men less than 40 years of age with a subacute or chronic onset
   (b) Men over 40 years of age with an acute or subacute onset
   (c) Women less than 40 years of age with chronic onset
   (d) Men less than 40 years of age with a subacute or chronic onset
   (e) Men over 40 years of age with a subacute or chronic onset

9. Which of the following is generally present in association with idiopathic lung fibrosis?

   (a) Hemoptysis
   (b) Uveitis
   (c) Clubbing
   (d) Pleuritic chest pain
   (e) Productive cough

10. Which of the following is not considered an idiopathic cause of DPLD?

   (a) Idiopathic pulmonary fibrosis
   (b) Hypersensitivity pneumonitis
   (c) Tuberous sclerosis
   (d) Amyloidosis
   (e) Sarcoidosis

Answer key: 1. (e), 2. (b), 3. (d), 4. (d), 5. (c), 6. (d), 7. (c), 8. (e), 9. (c), 10. (b)

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Part VII
Pulmonary Manifestations of Systemic Diseases

Chapter 15
Sarcoidosis

Massoud Mahmoudi and Om P. Sharma

Abstract Sarcoidosis is a common, multisystem granulomatous disease of unknown cause. The disease occurs worldwide, frequently affects young adults, and presents with bilateral hilar adenopathy, pulmonary infiltrates, uveitis, skin lesions, hypercalcemia, and hepatic granulomas. Diagnosis of sarcoidosis is based on the presence of typical multisystem clinical and radiographic features with histologic evidence of non-caseating granulomas in the affected tissue. Natural course of sarcoidosis varies with type of the disease: Acute sarcoidosis with erythema nodosum, uveitis, and bilateral hilar adenopathy clears with in a period of 12–18 months, particularly in the Caucasian patients; chronic disease with pulmonary infiltrate/fibrosis, lupus pernio, bone-cysts, nephrocalcinosis, chronic uveitis, and upper airway disease pursues an indolent course and respond minimally to treatment. Since the cause of sarcoidosis is not known; there is no specific cure for it. Corticosteroids are effective mode of therapy to suppress granulomatous inflammation, but they do not change the disease course.

Keywords Sarcoidosis • Tuberculosis • Granuloma • Hilar adenopathy • Uveitis • Extrapulmonary sarcoidosis • Non-caseating granuloma

Case 1

Our patient is a pleasant 42-year-old Caucasian male who initially presented to our clinic in February 2005 with a request for "check up and blood tests." Except seasonal allergies and some skin sensitivity he was doing well. His only medication included loratadine for seasonal allergies.

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Past medical history included seasonal allergies. His past surgical history included tonsillectomy as a child, appendectomy, and bilateral carpal tunnel surgeries. Social history: he denied smoking but admitted to social use of alcohol. Family history: Father had rheumatic fever and died of heart failure. Drug allergy: penicillin: red, itchy, swelling hands.

Review of systems. Except being nearsighted and one episode of syncope with negative workup was within normal limits.

Physical examination. He had hyperemic eyes, edematous nostrils, and rash in groin and genitalia.

Our plan included several laboratory tests: complete blood counts, lipid panel, thyroid hormones, hemoccult, and referral to a dermatologist. The results of laboratory test arrived few days later and except mildly elevated triglycerides and mildly reduced HDL, were within normal limits.

Approximately a year later, in March 2006, the patient returned with chief complaint of positional pain in abdomen and trunk during the night but resolving 5 min after getting up. The examination was within normal limits. Complete metabolic panel, complete blood counts, and urine analysis were ordered. The results arrived a few days later and all were within normal limits. In a later visit, the abdominal pain which had initially resolved had recurred. An abdominal ultrasound was ordered but was never done. We did not hear from the patient for 6 months until he presented with new symptom.

In September 2006, the patient presented with complaint of joint pain of 1 month duration and left arm pain for 2–3 weeks. Reportedly his previous abdominal pain had resolved.

The joint pain involved popliteal areas, ankles, elbows, shoulders, wrists, and hips. He reported that "I am not 100% since 2005."He reported feeling warm and sweating. On physical examination, the only abnormal finding consisted of ankle edema. Interestingly the joints were not tender to palpations. Initial blood work was ordered and he was asked to return for follow up. When he returned for evaluation, he was limping and still had ankle edema.

With Presented Data What Is Your Working Diagnosis?

Our initial impression was viral syndrome, polyarthralgia, and myalgia. However, the etiology of his condition was unclear to us.

Workup

Complete blood count (CBC): except mildly decreased lymphocytes (absolute numbers) was negative; C reactive protein (CRP): 14.32 (normal less than 5 mg/L); rheumatoid factor and antinuclear antibody (ANA): negative. Comprehensive metabolic panel: negative; Urine analysis: negative.

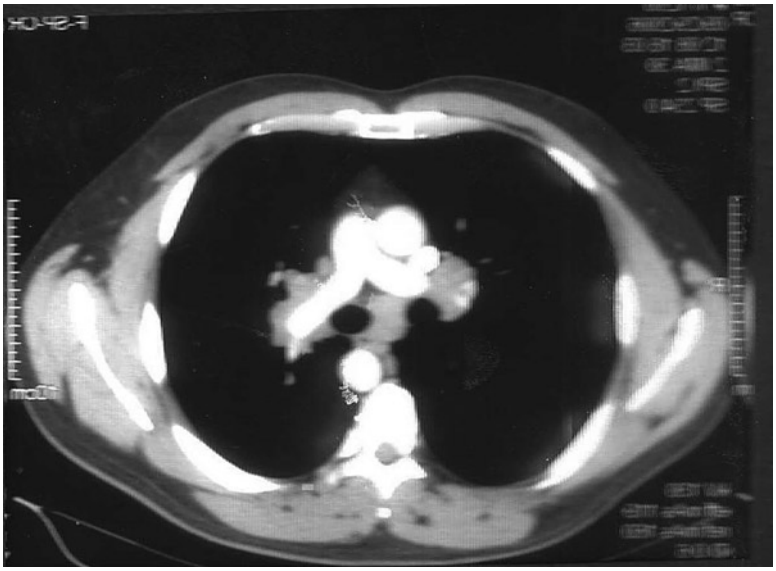

Fig. 15.1 Extensive superior mediastinal, subcarinal, and bilateral hilar adenopathy

Chest X-ray (PA and lateral) revealed: Slight prominence of hila (left greater than right).

Based on result of the chest X-ray, a CT scan of the chest was ordered. The results revealed extensive superior mediastinal, subcarinal, and hilar adenopathy (Fig. 15.1).

Differential diagnosis at this time included Lymphoma, metastatic seminoma, and sarcoidosis.

What Is Your Diagnosis and Why?

To narrow the diagnosis, we needed to further assess the nature of the adenopathy. In the mean time a laboratory test for Angiotensin Converting Enzyme (ACE) had revealed an elevated level. Next, the mediastinoscopy was performed and a large right peritracheal lymph node was biopsied. The pathological evaluation of the peritracheal lymph node was consistent with sarcoidosis. The patient presentation (the extrapulmonary symptoms), the imaging studies, the laboratory test, and finally the pathology of the tissue helped us to reach our final diagnosis of sarcoidosis.

Case 2

A 52-year-old African-American woman presented to emergency room with a history of substernal pain of 1 week duration. The pain was intermittent, did not radiate preferentially, and was not affected by exercise or change in position. However, the chest pain was often associated with diffuse abdominal pain. She had no dyspnea, hemoptysis, nausea, vomiting, jaundice, melena, or hematemesis.

On examination the patient was alert, articulate, and afebrile; vital signs were normal. She had multiple 2×2 non-tender movable lymph nodes in the anterior, posterior, and submandibular areas. Examination of the lungs and heart was normal. The abdomen was mildly distended with hyperactive bowel sounds; liver and spleen were not enlarged or tender. There was no point tenderness or rebound. The complete examination of the eyes, skin, and joints was normal.

Laboratory analysis revealed mild anemia of 11 g/dL. Complete metabolic panel, liver function tests, serum calcium, and serum angiotensin levels were within normal limits. Urine examination showed no red cells. An electrocardiogram showed normal sinus rhythm without ST-T wave changes.

With Presented Data What Is Your Working Diagnosis?

(1) Chest pain, (2) Abdominal Pain. The etiology of the presentation was unclear at this time and further workup was warranted.

Workup

Serial troponin levels were normal. A coronary angiogram showed a preserved ventricular function, normal coronary arteries, and a ventricular aneurysm. A chest x-ray film showed bilateral hilar and mediastinal adenopathy with no parenchymal infiltrate. A CT of the chest and abdomen showed thoracic, pericardial, peri-pancreatic, and omental lymph glands. A mediastinoscopy was performed; histological examination of the nodes showed non-caseating granuloma consistent with sarcoidosis. Acid-fast bacilli and fungal tests were negative.

What Is Your Diagnosis and Why?

Sarcoidosis involving the lungs (stage I). The imaging studies (X-ray and the CT of the chest) narrowed our diagnosis and the histological findings confirmed the diagnosis of the sarcoidosis.

Management and Follow-Up

Since the patient was symptomatic, she was started on a regimen of prednisone 40 mg daily. Over the course of a few months, her symptoms subsided. Serial CT scans showed reduced size of the multiple lymph nodes. She has been closely followed. After 2 years, she is asymptomatic.

Discussion

History

In 1877, Jonathan Hutchinson, a London general practitioner, described a patient with chronic multiple, raised, purplish cutaneous patches over hands and feet. This most likely was the first reported case of sarcoidosis. The term "Sarcoidosis" is credited to Caesar Boeck, who described histological findings of epithelioid cells and giant cells in skin biopsy and termed it "multiple benign sarkoid of the skin," implying that the histology resembled "sarcoma" of benign nature. Karl Kreibich of Prague drew attention to bone lesions and their association with lupus pernio. In 1909, Schumaker and Bering in 1910 first noted iritis accompanying cutaneous sarcoidosis. They also noted enlargement of the parotid and sub-maxillary salivary glands. At about the same time, Heerfordt, a Danish ophthalmologist, described the clinical association of uveitis, parotid gland enlargement, and the seventh nerve palsy. The syndrome of erythema nodosum and bilateral hilar adenopathy was recognized by a Swedish general practitioner Sven Lofgren.

Prevalence

Sarcoidosis, a multisystem disease, occurs worldwide. It has a high prevalence in Scandinavian countries, England, Ireland, North America, and Japan. In the developing countries of Asia and in Africa, the prevalence of the disease is not known because it remains hidden under the blanket of tuberculosis. In the past, syphilis was known a great masquerader; in the twenty-first century, however, sarcoidosis, because of its chameleon-like presentations, can safely be dubbed *la petite simulatrice*.

The disease commonly occurs in the third and fourth decades of life; it is infrequent in children and elderly. Families with several members affected with sarcoidosis are common as the likelihood of developing sarcoidosis ranges from 26 to 73 in individuals with a first-degree or second-degree family member with the disease. It is a genetically complex disease that involves not a single gene but multiple genetic

polymorphisms. There are several alleles that confer susceptibility to sarcoidosis (HLA DR 11, 12, 14, 15, 17); whereas, there are other alleles that offer protection (HLA DR1, DR4, and possibly HLA DQ 0202).

Pathogenesis and Pathology

The immunological alterations include depression of cutaneous delayed-type hypersensitivity, imbalance of CD4/CD8 T-cell subsets, an influx of T4 helper cells at the site of granulomatous activity, hyperactivity of B-cells, and the presence of circulating immune complexes. The initial reversible phase of the granulomatous inflammation is mediated by Th1 cytokines; the fibrotic phase is modulated by biological response modifiers released by the active macrophages that set the stage for remodeling of the lung tissue and inexorable fibrosis. Neutrophils, eosinophils, epithelioid cells, giant cells, and dendritic cells also participate. This drama is played in association with the class II major histocompatibility complex (MHC) region of chromosome-6. What initiates the process remains unknown. Could an unknown causative agents enter through the lungs? It would explain the presence of hilar adenopathy in more than 50% of the patients with sarcoidosis. Even at this early stage the evidence of granulomatous spread can be found in the liver and lung.

Diagnostic Workup

Recognize the Clinical Picture of Sarcoidosis

Because of its multisystem nature, sarcoidosis, like tuberculosis and systemic granulomatous diseases, often appears in the offices and clinics of general practitioners or family physicians, internists, and practitioners of various specialties who then refer these patients to chest physicians because of involvement of the lungs. Thus the burden of securing the accurate diagnosis and developing a therapeutic plan for various granulomatous illnesses usually falls on the shoulders of pulmonary specialists.

Sarcoidosis affects women more than men. The disease commonly attacks young adults and manifests with bilateral hilar adenopathy with or without pulmonary infiltration, reticulo-endothelial involvement, eyes, and skin lesions. Cardiac and central nervous system involvement are less frequent, but are more devastating. About 20–50% of the patients complain of dyspnea, cough, chest tightness or pain. Blurring of vision, red-eye, photophobia, and loss of visual acuity occur in less than 20% of the patients. Lofgren's syndrome, a combination of erythema nodosum and bilateral hilar adenopathy, is a manifestation of acute sarcoidosis. The combination of parotid gland enlargement, uveitis, and facial nerve involvement is called Heerfordt syndrome. Lupus pernio, the hallmark of chronic sarcoidosis, is often associated with bone lesions, chronic uveitis, and pulmonary fibrosis. Hypercalcemia

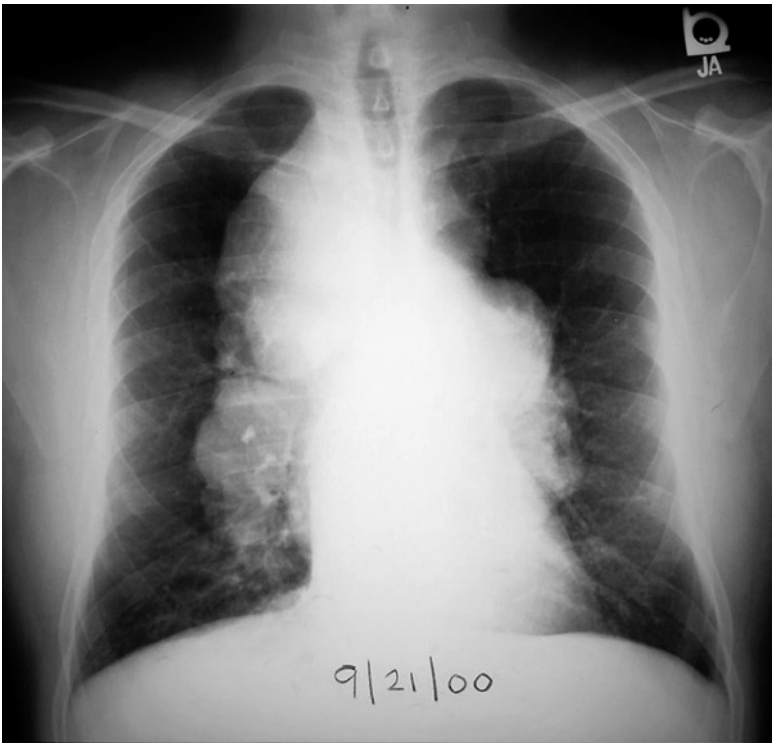

Fig. 15.2 Stage I sarcoidosis: extensive hilar and mediastinal adenopathy

is seen in about 10% of the patients; whereas hypercalciuria is three times more common. Fatigue, polyuria, thirst, arthritis, heart block, mono-or polyneuritis, small nerve involvement, muscle weakness, or anemia may occur. Sarcoidosis is an iceberg syndrome, for many forms of the disease remain undetected. Clinician must dig deeper to uncover the latent and clinically hidden forms of sarcoidosis.

Recognize the Chest X-Ray Abnormality

More than 90% of the patients have an abnormal chest x-ray picture. In about 5–10% of patients the chest x-ray film is normal, but even in these patients HRCT may uncover characteristic abnormalities. Conventionally, intra-thoracic abnormalities are classified as follows:

Stage 1 Bilateral hilar or mediastinal adenopathy (BHL) (Fig. 15.2)
Stage 2 BHL with parenchymal infiltration;
Stage 3 Parenchymal infiltration without BHL (Fig. 15.3)
Stage 4 Bullous, cystic and emphysematous changes (Fig. 15.4). Computed tomography (CT) can depict additional mediastinal and thoracic nodes that are not visible

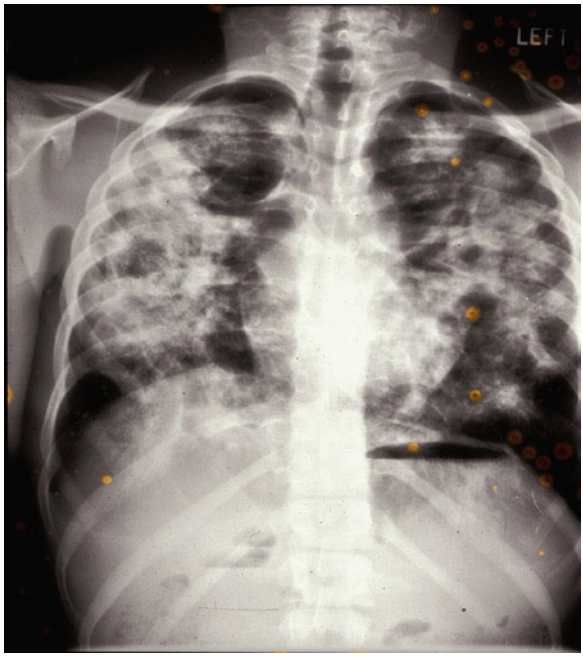

Fig. 15.3 Stage III sarcoidosis: extensive pulmonary infiltrate in a 33-year-old woman

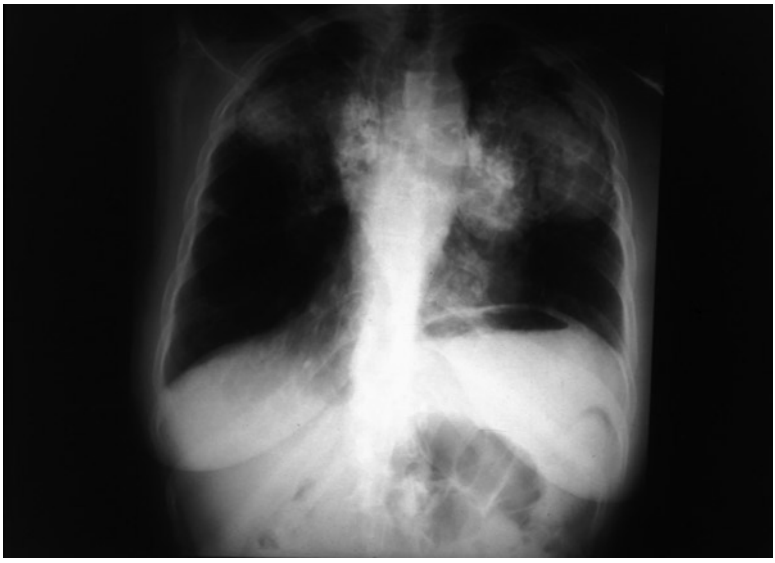

Fig. 15.4 Stage IV sarcoidosis with lung destruction and massive aspergillomas

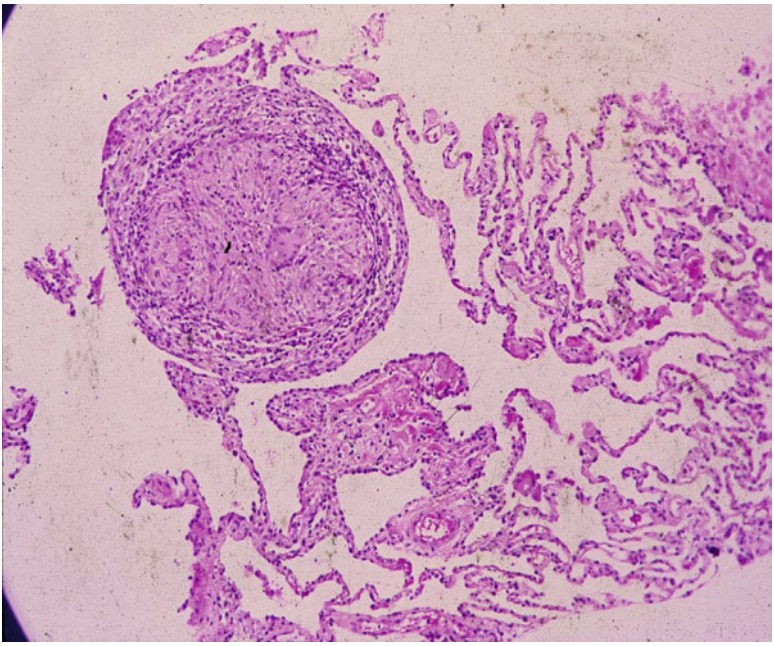

Fig. 15.5 Sarcoidosis: a non-caseating granuloma

on a chest radiograph. High-resolution CT (HRCT) is helpful in assessing the parenchymal abnormalities including nodules along bronchovascular bundles (beading), particularly in the mid and upper lung fields, pleural or sub-pleural nodules, septal lines, confluent opacities with air-bronchograms, cystic or bronchiectatic lucencies, honeycombing, and bullae formation. Despite the accuracy and availability of CT and HRCT, routine use of these tests in the management of sarcoidosis is neither necessary nor cost-effective. Magnetic resonance imaging (MRI) is helpful in evaluating the extent of damage in neuro-sarcoidosis and, to a lesser degree, in myocardial involvement.

Secure the Histological Evidence of Non-caseating Granuloma

When confronted with a suggestive clinical/radiologic picture of sarcoidosis, it is important to obtain histologic confirmation. Fiber-optic bronchoscopy is the most helpful diagnostic procedure. Aspiration liver biopsy, not commonly used, is a quick and convenient method to obtain histologic confirmation. If serial sections are cut throughout the biopsy then hepatic granulomas are observed in about two-thirds of biopsies. Alternatives sites depend upon the tissue involved. They include peripheral lymph nodes, skin, nasal mucosa, conjunctiva, lacrimal and salivary glands, muscle, and spleen. The histopathologic hallmark of sarcoidosis is a compact, round or oval granuloma made up of radially arranged epithelioid cells with pale-staining nuclei. Lymphocytes found in the granuloma are usually seen at the periphery (Fig. 15.5).

The giant cell of the sarcoid granuloma may be of Langhan's or of the foreign-body type. Caseation is absent. Minor degrees of fibrinoid necrosis may be seen; extensive necrosis, however, is rare. Asteroid, Schaumann, and Hamasaki-Wesenberg bodies are frequently found within the epithelioid and giant cells. The structural arrangement of the granuloma is an example of perimeter defense seen in other infectious and non-infectious diseases; however, no single agent has ever been either consistently shown or cultured from sarcoidosis granulomas.

Biopsy specimens should be submitted to microscopic examination, culture, chemical analysis, and nucleic acid amplification.

The histological evidence of non-caseating granulomas can be produced by many bacteria including tuberculosis and leprosy, fungi, parasites, and organic dust diseases. *Mycobacterium tuberculosis* is one of the most frequent causes of an infective granulomatous response. The hallmark of tuberculous lesion is a central area of caseation. In patients with good resistance against the organism the granulomas remain discrete and non-caseating and may be indistinguishable from those seen in sarcoidosis. Under these circumstances it is essential to detect the organism by special staining and culture. All clinical specimens labeled sarcoidosis must be cultured for mycobacteria.

It should, however, be emphasized that a large number of other diseases can cause a histological appearance similar to that seen in sarcoidosis and tuberculosis (Table 15.1). Fungi are an important cause of granulomas in many surgical pathology practices in the world. Coccidioidomycosis caused by *Coccidioides immitis* is endemic in San Joaquin Valley in California and histoplasmosis caused by *Histoplasma capsulatum* has much wider distribution. Infectious granulomas are most commonly necrotizing. The infectious granulomas may be solitary or multiple in location, and broncho-centric, alveolar, lymphangitic or vascular in distribution The presence of neutrophils or eosinophils within the necrotic foci or adjacent tissue should suggest fungal or mycobacterial infection. Sometimes mycobacterial infections caused by *M. tuberculosis* or bovis produce problems related to small size of the biopsy specimen. While Ziehl-Neelsen stains demonstrate acid-fast organisms in as many as 77% of large solitary necrotizing granulomas, but they usually fail to show organisms when granulomas are non-necrotizing or hyalinized, particularly in small biopsy specimens, such as obtained via fiberoptic bronchoscopies or from intra-thoracic needle biopsies. Other forms of non-tuberculous mycobacterial infections can cause granulomatous pulmonary disease resembling sarcoidosis, e.g., in an immunocompetent host, *M. avium-intracellulare* can cause a predominantly non-necrotizing granulomatous pneumonitis.

Laboratory Tests to Support the Diagnosis

New techniques, as they emerge, help to detect new features of the disease. When fluorescence angiography was introduced, it revealed leaking retinal veins. Serum angiotensin concerting enzyme (ACE) levels and Gallium scanning are helpful in monitoring the disease; they have little value is establishing the diagnosis.

Table 15.1 Usual causes of granuloma formation

Bacteria
M. tuberculosis
Atypical mycobacteria
M. leprae
Brucella sp.
Spirochetes
Viruses
Rickettsia
Fungi
Histoplasma capsulatum
Coccidioides immitis
Cryptococcus neoformans
Blastomyces dermatitidis
Paracoccidioidomycosis
Parasites
Toxoplasma
Leishmania
Schistosoma
Trichinella
Minerals
Beryllium, zirconium, cobalt
Talc, silica
Organic antigens
Thermophilic actinomycetes
Avian antigens
Local sarcoid reactions
Lymphoma, carcinoma
Crohn's disease
Primary biliary cirrhosis
Necrotizing sarcoid granulomatosis
Vasculitis

High-resolution CT and MRI scans with Gadolinium enhancement have brought a new dimension to visualizing cardiac and neuro-sarcoidosis. It is to be hoped that nuclear imaging and MRI studies will uncover latent myocardial sarcoidosis. PET scanning is helpful in detecting and monitoring myocardial sarcoidosis in patients with pacemaker or defibrillator on whom MRI cannot be used.

Tuberculin Test

Tuberculin test is negative in more than two-thirds of the patients. At the onset of sarcoidosis a previously positive tuberculin test becomes negative and with cure of the disease it tends to revert to its original responsiveness. A strongly positive tuberculin test is rare in sarcoidosis.

Table 15.2 Differences between sarcoidosis and tuberculosis

Features	Tuberculosis	Sarcoidosis
Age (years)		20–50
Fever, weight loss	Common	Rare
Erythema nodosum	Uncommon	Common
Uveitis	Uncommon	Common
Skin involvement	Rare (lupus vulgaris)	Common (lupus pernio, plaques)
Pleural effusion	Common	Rare
Involvement of small intestine	Common	Rare
Granulomas	Caseating	Non-caseating
Acid fast bacilli	Present	Absent
Tuberculin test	Positive in most	Negative in most
Kveim–Siltzbach test	Negative	Positive
Serum Angiotensin Converting Enzyme (ACE)	Elevated in 5–10%	Elevated in 60%
Hypercalcemia/hypercalciuria	No	Yes
Hilar adenopathy	Unilateral	Bilateral
Pulmonary infiltrate	Usually unilateral	Usually bilateral
Ghon focus	Yes	No
Antituberculosis drugs	Treatment of choice	Unhelpful
Corticosteroids	May be harmful alone	Helpful
Worldwide distribution	Shrinking	Increasing

Strict adherence to these diagnostic workup presents practical problems particularly in the developing countries. First, the patient, particularly when asymptomatic, may not be willing to have any invasive procedure carried out. Secondly, biopsy procedures depending on the site and technique carry definite, albeit small, risk of morbidity and even mortality. Finally, trained personal and well equipped laboratories and bronchoscopy facilities required to carry out these procedures are not available to the majority of world population. Consequently, sarcoidosis patients are misdiagnosed and inappropriately treated as tuberculosis and vice versa. Nevertheless, clinical, radiological, and laboratory difference between the two disorders are many and a reasonable diagnosis can be made if simple instructions are followed (Table 15.2).

Indications for Treatment

Pulmonary Sarcoidosis

1. Asymptomatic patient with bilateral hilar lymphadenopathy (Stage I) with or without erythema nodosum but without extra pulmonary involvement should be left untreated.

2. Patients with fever and joint pains respond to non-steroidal anti-inflammatory agents. Occasionally, a short-term course of prednisone 15–20 mg/day may be needed to control symptoms that do not respond to anti-inflammatory drugs. Symptoms of cough and dyspnea may be associated with airway obstruction – even in this early stage – and should be treated with inhaled corticosteroids.
3. Patients with bilateral hilar adenopathy and infiltration (Stage II) and symptoms (cough, dyspnea, chest pain, and effort intolerance) should be treated. Spirometry, diffusing capacity, a chest radiograph, and serum ACE should be used to monitor the course of the disease.
4. Patients with Stage II who are asymptomatic and have only mild lung function impairment can be followed without any specific treatment. However, if deterioration of lung function should occur over a period of 3–6 months, the treatment should be instituted.
5. Patients with Stage II who are asymptomatic with severe lung function impairment should be treated. Serial lung function measurement should be performed to establish the maximum response prior to tapering the drug to the maintenance dose.
6. Patients with Stage III disease with diffuse pulmonary infiltration usually have symptoms along with lung function abnormalities and almost always need treatment. Asymptomatic stage III patients with progressive pulmonary function impairment may respond to corticosteroids because of the presence of reversible alveolitis intermingled with diffuse fibrosis.
7. Stage IV diseases with extensive fibrosis and bullae formation respond poorly or not at all to corticosteroids and immunosuppressive therapy. It should however be emphasized that some stage III and IV patients with irreversible fibrosis may have coexisting active alveolitis and the treatment should be strongly considered in order to control symptoms and functional impairment. Some of the patients with stage IV disease are ideal candidates for lung transplantation. Bronchiectasis, hemoptysis, and aspergilloma are treated conservatively with appropriate antibacterial and antifungal agents. An occasional patient with aspergilloma causing hemoptysis can benefit from intracavitary instillation of antifungal agents or arterial embolization. Resection may be necessary for severe hemoptysis if lung function is not severely impaired.

Extra-Pulmonary Involvement

Involvement of extra-pulmonary sites is common and often of major clinical importance. Constitutional symptoms of fever, night sweats, weight loss, fatigue, myalgia, and arthralgias occur frequently with extrathoracic sarcoidosis. Fatigue, in particular, is an important symptom. Although any organ can be involved, skin and eye are most common, whereas cardiac and neurological involvement is most serious. Major extrapulmonary manifestations of sarcoidosis are outlined below, detailed descriptions can be found elsewhere.

Skin

Erythema nodosum, subcutaneous nodules and plaques, lupus pernio and maculopapular eruptions are the important manifestations of sarcoidosis. Specific lesions demonstrate granulomatous inflammation on biopsy. Nonspecific skin lesions are inflammatory skin reactions with no evidence of granulomatous inflammation. Erythema nodosum (EN) is the most common nonspecific skin lesion of sarcoidosis. It presents as tender nodules on the extremities. EN with hilar lymphadenopathy (Löfgren's syndrome) also often with polyarthropathy and nongranulomatous uveitis is a typical subset of sarcoidosis. The most common specific lesions are firm, 2–5-mm papules that often have a translucent red-brown or yellow-brown appearance. Lupus pernio affects the nose, cheeks, lips, and ears in form of indolent, red-purple, or violaceous skin lesions. Lupus pernio is associated with poor prognosis of sarcoidosis and is associated with more severe pulmonary disease.

Eyes

Eyes are involved in sarcoidosis in up to 25% patients. Ocular manifestation can be the early or major manifestation of the disease. Any part of the eye can be affected. A careful eye check-up by an ophthalmologist should be a part of routine workup of every patient of sarcoidosis. Depending upon the site of involvement the symptoms vary from blurred vision, red eye, painful eye, or photophobia in anterior uveitis to retina vision loss in posterior uveitis. Uveitis is the most common ocular manifestation of sarcoidosis. One-third of the patients with anterior uveitis have no symptoms. Besides uveitis, involvement of lachrymal glands is also common, which may occasionally cause dry eyes. Optic neuropathy is rare but can result in rapid, permanent vision loss. Funduscopic examination may show retinal perivasculitis, retinal scarring, glaucoma, papillitis, papilledema, neo-vascularization, and optic atrophy.

Heart

Although rare, cardiac or neurologic sarcoidosis may be life threatening. Therefore, it is important to recognize it early. Clinically detectable in only 5% of sarcoidosis patients, cardiac involvement may be picked up in 25% subjects at autopsy.

Cardiac sarcoidosis may cause left ventricular dysfunction, cardiac arrhythmias, and sudden death. Endomyocardial biopsy is the gold standard, but it has a sensitivity of less than 20%. For the non-invasive diagnosis of cardiac sarcoidosis various investigations including echocardiography, thallium scanning, gallium scanning, MRI, or PET scanning are used singly or in combination.

Central Nervous System

Sarcoidosis mimics diverse neurological conditions. Diagnosis of neurosarcoidosis is based on a confirmation of systemic sarcoidosis since pathologic confirmation is

rarely available from the central nervous system (CNS). Overall CNS involvement may be seen in about 10% patients of sarcoidosis. The most common manifestation of neurosarcoidosis is seventh cranial nerve palsy, and it may precede the diagnosis of the disease. It may affect any part of the nervous system causing a cranial nerve palsy, mononeuropathy or polyneuropathy, aseptic meningitis, seizures, mass lesions in the brain or spinal cord, and encephalopathy.

Indications for the treatment of extrapulmonary involvement sarcoidosis are relatively straightforward. Ocular, neurologic, cardiac, upper airway involvement and hypercalcemia almost always need corticosteroids, often in higher doses (60–80 mg), and for a long time. Glandular involvement, splenic enlargement, parotid swelling, and cutaneous lesions respond to modest doses of 20–30 mg daily. Asymptomatic hepatic involvement usually requires no therapy, but regular follow-up evaluation must be provided to exclude progressive impairment of liver function.

Therapy and Drugs

There is no single cure for sarcoidosis.

Corticosteroids

The ATS/ERS/WASOG statement recommends an initial dose of 20–40 mg/day for pulmonary sarcoidosis, or its equivalent on alternate days. The authors suggest that the patients be evaluated every 1–3 months. In steroid responders dose is gradually tapered to 5–10 mg/day (or an equivalent alternate dose), and are treated for a minimum of 12 months. Inhaled steroids are of value in patients with airway disease. Higher doses of 60–80 mg daily are needed to control severe ocular, neurologic, myocardial lesions, and malignant hypercalcemia. If a relapse occurs, as evidenced by reappearance of clinical signs, chest radiograph abnormality, lung function impairment or markedly elevated angiotensin converting enzyme, the dose is then increased to the high dose sufficient to control the disease. The drug is then reduced to a maintenance dose that is likely to be higher than the dose at which the relapse had occurred. Although alternate-day regimen is effective with considerable reduction of side effects, daily treatment is recommended because of increased compliance. Relapses are common and may occur in 20–50% cases following discontinuation of the treatment. Thus, many patients with recurrent relapses need treatment for prolonged periods, sometimes for years. Complications, particularly weight-gain, diabetes, ocular cataract, and necrosis of the hip occur but with reduced frequency if corticosteroids are used in moderate doses described here.

Methotrexate

The beneficial affects of methotrexate were seen in the patients with lupus pernio, other disfiguring skin lesions, and chronic systemic disease where corticosteroids

had caused significant side-effects. Methotrexate does not have any direct effect on T-cell function, but it alters peripheral blood-derived macrophage function. In experimental models methotrexate suppresses B-cell function as assessed by immunoglobulin production. The specific toxicity of methotrexate is the liver damage. It is a dose-dependent phenomenon, because the patients who do receive the cumulative dosage of greater than 1.0 g seldom develop liver toxicity. Routine liver function tests may not detect the early, reversible, changes of methotrexate toxicity; a liver biopsy is often recommended to diagnose the damage. Hypersensitivity pneumonitis may occur in the patients receiving methotrexate. The estimated frequency is as high as 1%, especially in the patients treated for years. Usual dose of methotrexate is 15 mg weekly. Sometimes, it may take up to 6 months for the drug to be effective. Folic acid is given concurrently to avoid hematological toxicity.

Hydroxychloroquine

Chloroquine and hydroxychloroquine have anti-inflammatory activity, especially in rheumatoid arthritis. In sarcoidosis these drugs seem to interfere with the processing of the putative antigen by macrophages. In cutaneous sarcoidosis, these drugs seem to have about a 35% response rate. Chloroquine and hydroxychloroquine switch off the production of the vitamin-D metabolite from granulomas and active macrophages. The toxicity of both these drugs includes nausea and gastrointestinal discomfort which can be avoided by taking the drug with meals. The patients who find it hard to tolerate the recommended dose of 200 mg of hydroxychloroquine twice daily may derive benefit from a 200 mg once a day regimen.

Retinal toxicity is infrequent with hydroxychloroquine. If the patient has any history of retinal disease, either attributable to sarcoidosis or another condition, these drugs should be avoided. Eye examination is recommended while the patient is on treatment, usually every 6–12 months when using hydroxychloroquine.

Azathioprine

Azathioprine (Imuran) is converted to 6-mercaptopurine in the body. The drug is reserved for severe, refractory cases of extrapulmonary sarcoidosis. The usual dose of azathioprine is 2–3 mg/kg of weight body weight daily by mouth.

The drug's active metabolite 6-mercaptopurine is metabolized by a methyl transferase. A small percentage of the population lacks an active phenotype of the enzyme, leading to excess levels of 6-mercaptopurine. The effect is apparent within the first 2 weeks of treatment. The patient without the enzyme has prolonged and significant bone marrow toxicity. By initiating therapy at the relatively low dose of 50 mg per day, one should be able to determine the patient's sensitivity to azathioprine within the first month. Routine follow-up should include monthly complete blood counts and renal function tests.

5 Chlorambucil

Another alkylating agent, chlorambucil, has been used in some sarcoidosis patients. Its mechanism of action is similar to that of the other cytotoxic agents. Because of its relatively high toxicity and apparent lack of benefit for refractory cases such as those with neurosarcoidosis, its use is limited.

Cyclophosphamide

Cyclophosphamide, another immunosuppressive agent, has been used in treating cardiac or renal sarcoidosis, patients who failed corticosteroids. A few case reports suggest the drug may be useful for neurosarcoidosis. The drug can be given orally 50–150 mg daily or 50–2,000 mg intravenously every 2 weeks. Cyclophosphamide can lead to alopecia, hemorrhagic cystitis. With chronic use for at least a year, cystitis occurs in 5–10% of patients. If cystitis occurs, the cyclophosphamide must be discontinued.

Cyclosporine

This has marked effects on T-helper cells. The toxicity of cyclosporine includes hypertension, renal failure, and increased risk of blood cancers.

Ketoconazole

This antifungal agent has been proven to help patients with hypercalcemia caused by sarcoidosis. It inhibits several enzymes in the cytochrome P450 enzyme system, the production of steroid hormones, and the production of 1, 25-dihydroxyvitamin D.

Radiation Therapy

This type of treatment has been used in a limited number of patients with sarcoidosis, most often in those with uncontrolled, progressive neurologic disease.

Non-steroidal Anti-inflammatory Drugs

They are useful in treating joint pains and aches associated with erythema nodosum and other forms of mild disease. James et al. performed a randomized trial comparing oxyphenbutazone, prednisone, or placebo. The authors found both agents were significantly better than placebo.

Thalidomide

Thalidomide has an anti-TNF activity. It has been found to be effective in chronic cutaneous sarcoidosis. Unfortunately sedation and neurological side effects limit the use thalidomide.

Pentoxifylline

It is of benefit in the patients with sarcoidosis. The agent is well tolerated by most patients. Gastrointestinal distress is the most common reported toxicity

Infliximab

Infliximab is a chimeric IgG monoclonal antibody against TNF-alpha. It binds both the soluble and transmembrane forms of TNF-alpha. It is effective in treating Crohn's disease and rheumatoid arthritis. This antibody has no action against TNF-beta, a related cytokine. I have treated ten patients of sarcoidosis with infliximab. These patients had either not responded to other drugs or had developed severe side effects to corticosteroids. The remarkable response of cutaneous, bone, and neurosarcoidosis warrants further double blind studies.

Summary

There is no absolute cure for sarcoidosis. This state will last until we find the cause of sarcoidosis. Meanwhile, many more therapeutic agents will emerge that will benefit sarcoidosis patients. In treating sarcoidosis patients one should be careful not to use agents with high toxicity particularly in the patients with benign or limited sarcoidosis.

Questions

1. Which of the following are the causes of chest pain in sarcoidosis?
   (a) Musculoskeletal
   (b) Gastrointestinal
   (c) Cardiac
   (d) Pulmonary
   (e) All of the above

(e) All of the above. In descending order of prevalence, the causes of chest pain are musculoskeletal (36%), gastrointestinal (16%), cardiac (16%), psychiatric (8%), pulmonary (5%), and unknown factor (16%) [1]. Nevertheless, the frequency varies and depends on the population studied. Myocardial infarction, aortic dissection, tension pneumothorax, pulmonary infarction, esophageal rupture, and acute abdomen are some of the potentially life threatening causes. After extensive evaluation (case 2), we concluded that the patient was most likely related to either enlarged hilar, mediastinal, or pericardial lymph nodes or to the left ventricular aneurysm or both

2. Which statement regarding the chest pain in sarcoidosis is true?

(a) Non-specific chest pain is not uncommon in sarcodidosis
(b) Chest pain may be correlated with radiologic stages of the disease
(c) The chest pain in sarcoidosis may be sub-sternal, intracapsular, or pleurritic in nature
(d) All of the above
(d) All of the above. Non-specific chest pain is not uncommon in sarcoidosis. In a study of 821 sarcoidosis subjects, 19% had chest pain [2]. The nature of chest pain not explained. Smedema and colleagues correlated chest pain with radiological stage of the disease [3]. They found no relationship. Hendricks et al., on the other hand, contended that that the enlarged hilar nodes could cause chest pain not too dissimilar from that of coronary disease [4]. The pain described with sarcoidosis can be sub-sternal, intracapsular or pleuritic in nature. Curiously in lymphoma enlarged nodes can cause not only the pain, but the pain may also worsen after drinking a few glasses of alcohol. This interesting sign is called Hoster sign [5]. I reported the occurrence of Hoster's sign in sarcoidosis more than 30 years ago [6]

3. Which one of the following may be a clinical presentation in symptomatic cardiac sarcoidosis?

(a) Congestive heart failure
(b) Ventricular and supraventricular arrhythmias
(c) Conduction abnormalities
(d) Sudden death
(e) All of the above
(e) All of the above. Symptomatic cardiac sarcoidosis occurs in about 5% of sarcoidosis patients. Clinical presentations include congestive heart failure, ventricular and supraventricular arrhythmias, conduction abnormalities and sudden death. Coronary angiography is usually normal, but when granulomatous vasculitis is present then the evidence of thrombosis and aneurysm can be observed. MRI has a sensitivity of 100% and specificity of 78% for the diagnosis of sarcoidosis. Late mycocardial enhancement is typical, but various patterns of injury have been described . In a necropsy study, Roberts and colleagues found aneurysms in 9 out of 86 subjects [7]. Ventricular aneurysms without evidence of coronary artery disease have been described in sarcoidosis [8]

4. Which of the following warrants treatment?

   (a) Asymptomatic patient with hilar adenopathy (Stage I)
   (b) Patient with bilateral hilar adenopathy and infiltration (Stage II) and symptoms (cough, dyspnea, chest pain, and effort intolerance)
   (c) Patient with Stage II who is asymptomatic and have only mild lung function impairment
   (d) Patient with Stage II who are asymptomatic with severe lung function

5. Which one of the following is important manifestation of sarcoidosis?

   (a) Erythema nodosum
   (b) Subcutaneous nodules and plaques
   (c) Lupus pernio
   (d) Maculopapular eruptions
   (e) All of the above

6. Which one of the following is the most common ocular manifestation of sarcoidosis?

   (a) Uveitis
   (b) Keratoconjunctivitis
   (c) Proptosis
   (d) Involvement of lachrymal gland
   (e) E-Optic neuropathy

7. Which one of the following features about sarcoidosis and tuberculosis is true?

   (a) Granuloma is non-caseating in Tuberculosis and caseating in Sarcoidosis
   (b) Fever and weight loss are common in Sarcoidosis and rare in Tuberculosis
   (c) Uveitis is common in Sarcoidosis and uncommon in Tuberculosis
   (d) Kevim-Siltzbach test is positive in tuberculosis and negative in Sarcoidosis

8. Which of the following organism is a usual cause of granuloma formation?

   (a) Toxoplasma
   (b) *Leishmania*
   (c) *Cryptococcus neoformans*
   (d) *Mycobacterium tuberculosis*
   (e) All of the above

9. All of the statements regarding Sarcoidosis is true except:

   (a) Sarcoidosis is a common, multisystem granulomatous disease of unknown cause
   (b) There is no absolute cure for Sarcoidosis
   (c) Uveitis is uncommon in Sarcoidosis
   (d) Erythema nodosum is common in Sarcoidosis

10. Which one of the statement regarding sarcoidosis is correct?
    (a) Overall CNS involvement may be seen in 30% of the patients with Sarcoidosis
    (b) Eye involvement in Sarcoidosis is up to 2%
    (c) Stage IV disease with extensive fibrosis and bullae formation are good responder to corticosteroids
    (d) Hilar adenopathy is unilateral in Tuberculosis and bilateral in Sarcoidosis

Answer key: 1. (e), 2. (d), 3. (e), 4. (b) and (d), 5. (d), 6. (a), 7. (c), 8. (e), 9. (c), 10. (d)

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Chapter 16
Cystic Fibrosis

Elliott C. Dasenbrook

Abstract Cystic fibrosis is a multisystem disease that occurs due to a dysfunctional anion channel in epithelial cells. In the lungs, this leads to a vicious cycle of airway obstruction, infection, and inflammation that leads to progressive respiratory decline and death. Here, we present two challenging cases of patients with progressive respiratory decline associated with failure to respond to standard treatment for a pulmonary exacerbation.

Keywords Cystic fibrosis • *Mycobacterium abscessus* • *Nocardia farcinica* • *Pulmonary nocardia* • Tree-in-bud pattern • *Pseudomonas aeruginosa* • Dysfunctional anion channel in epithelial cells

Case 1

Our patient is a 28-year-old Caucasian female with cystic fibrosis (CF), who presents with a complaint of increased coughing associated with increased sputum production over the last 3 weeks. Her sputum is thick and dark yellow, but she does not report any hemoptysis. In addition, she has noticed low-grade fevers and increased fatigue. She has not had any change in her appetite. She was on oral doxycycline for 2 weeks with slight improvement in her symptoms. However, when the course finished, her symptoms worsened again. She has a history of CF, which was diagnosed in infancy after presenting with recurrent pulmonary infections. The sweat chloride was 94 mEq/L (a sweat chloride level greater than 60 mEq/L is consistent with a diagnosis of CF) and she had one "mild" mutation and one "severe" mutation. Her cystic fibrosis has

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been complicated by early lung disease with mild bronchiectasis and a baseline forced expiratory volume in 1 s (FEV_1) percent predicted of 95%, chronic colonization with methicillin-sensitive *Staphylococcus aureus* (MSSA), an asthmatic component to her cystic fibrosis, and recurrent sinusitis. Other than when she was originally diagnosed, she has never required intravenous antibiotics for a pulmonary exacerbation. She is pancreatic sufficient. She regularly does airways clearance and runs 3 miles every day. She is intolerant of trimethoprim/sulfamethoxazole and has no known drug allergies. She does not have any siblings with CF. She is married and has one young child who attends daycare and the child has recently had a "cold". She works from home, but her job requires her to travel via airplane twice a month. She has not recently been outside of the continental USA. She does not smoke cigarettes or use illicit drugs. She drinks 1–2 glasses of wine per week.

Review of systems. Her sinus symptoms are at their baseline. Other than a decreased appetite associated with a 2 lb weight loss and increased fatigue, her review of systems was unremarkable.

Physical examination. She appeared as a pleasant female, well nourished and in no acute distress. Vitals: BP 122/76 mmHg, pulse: 81 beats/min (regular), and oxygen saturation was 98% while breathing ambient air. HEENT: Other than some mild congestion of her B nasal turbinates, unremarkable. Neck: No lymphadenopathy. Heart: regular rhythm with no murmur. Chest: she was not barrel chested. No retractions or use of accessory muscles. Clear to auscultation throughout without crackles or wheezes. Abdomen: normal bowel sounds. No masses or organomegally. Extremities: 1+ clubbing, pink. The rest of the exam was within normal limits.

Diagnostic testing. MSSA was detected from an expectorated sputum sample. Spirometry revealed that her FEV_1 had dropped 14% points to 81% predicted.

Impression. The patient has an increase in her baseline respiratory symptoms in conjunction with fatigue and weight loss. In addition, she has had a greater than 5% drop in her FEV_1 percent predicted. Therefore, she meets criteria for a cystic fibrosis pulmonary exacerbation.

Plan. We recommended a course of intravenous antibiotics given the significant respiratory symptoms that did not resolve after a course of oral antibiotics.

With Presented Data, What Is Your Working Diagnosis?

The pulmonary exacerbation is most likely due to MSSA, anaerobic infection, or a viral infection (perhaps from her daughter).

The intravenous antibiotics were chosen based on the antibiogram from her most recent MSSA culture. In addition, we chose an antibiotic that also had activity against anaerobes, since CF patients frequently have anaerobic bacteria in their

sputum. A PICC line was placed and the initial doses of antibiotics were tolerated. Her admission labs were all within normal limits and revealed normal liver and kidney function. A posteroanterior and lateral chest roentogram revealed mild bronchiectasis of the left upper lobe. Her admission bacterial respiratory culture grew out MSSA sensitive to our initial antibiotic choice. On day #2, the lab called to state that 1+ acid fast bacilli (AFB) were observed on the AFB smear. Soon thereafter, the *Mycobacterium* species was identified as a rapid grower.

Differential diagnosis. Rapid grower species of *Mycobacterium* were added to the differential diagnosis and include: *M. fortuitum*, *M. abscessus*, and *M. chelonae*.

Workup

We treated the patient with 2 weeks of IV antibiotics targeting the MSSA and anaerobes. Her symptoms improved, but did not fully return to baseline. Over the next 2 months, the rapid grower species and the susceptibility pattern were identified. The AFB analysis identified the rapid grower species as *Mycobacterium abscessus*. The in vitro susceptibility pattern was performed at a reference laboratory and the patient's strain of *M. abscessus* was susceptible to amikacin and clarithromycin. Two repeat AFB analyses were performed over a 3-month period (both expectorated sputum samples) and both were again positive for *M. abscessus*. We obtained a high resolution computed tomography (CT) scan of the chest and she had mild bronchiectasis in the RUL, a tree-in-bud pattern in the bilateral upper lobes, but no cavities or focal nodular disease. A previous CT chest was not available for comparison.

The goal of IV antibiotic therapy is for the patient to return to their baseline status. At baseline, our patient has a dry cough that occurs a couple times per day. However, at the conclusion of IV antibiotics targeting her MSSA, she was still coughing throughout the day and was occasionally productive of thin, light yellow sputum. Her FEV_1 improved to 88% predicted, but was still well below her baseline.

What Is Your Diagnosis and Why?

We diagnosed the patient with *M. abscessus* lung disease. The patient met both clinical and microbiologic American Thoracic Society/Infectious Disease Society of America criteria for the diagnosis of nontuberculous mycobacterial (NTM) lung disease (Table 16.1) [1]. Clinical and microbiologic criteria are both required to make the diagnosis. She met the clinical criteria because she had pulmonary symptoms (cough, sputum production, low-grade fevers, and CT findings consistent with NTM) that did not resolve with treatment of her other CF pathogens, thus we had excluded other diagnoses. She met the microbiologic criteria because she had more than two positive expectorated sputum samples that were 2 months apart.

Table 16.1 Diagnosis of nontuberculous mycobacterial lung disease

Clinical	
1. Pulmonary symptoms, or chest radiograph, or high resolution CT scan	Nodular or cavitary opacities, multifocal bronchiectasis with multiple small nodules
2. Exclusion of other diagnoses	
Microbiologic	
1. Expectorated sputum, or	At least two separate samples
2. Bronchial wash or lavage, or	At least one sample
3. Lung biopsy	Histopathology and culture consistent with mycobacterial disease.
Caveats	
Consider expert consultation for difficult diagnoses	
If suspicion high and tests nondiagnostic, then follow patient closely until diagnosis resolved	
A diagnosis does not automatically imply therapy. Risks and benefits in each individual patient should be determined.	

Adapted from Griffith and colleagues [1]

Discussion

One important caveat to the diagnosis of *M. abscessus* lung disease is that diagnosis of NTM does not automatically imply treatment. The benefits of treating the infection and preventing morbidity and mortality must be weighed against the significant toxicities of the long-term treatments required. The spectrum of *M. abscessus* lung disease in CF includes patients with a slowly progressive course with minimal changes over years of follow-up to more severe courses associated with rapid worsening of lung disease and death. After discussing her individual case and the potential toxicities of the numerous antibiotics used in the treatment of *M. abscessus*, our patient's strong preference was to initiate therapy because (1) she had a friend with CF whose respiratory status declined rapidly after the diagnosis of *M. abscessu*s and (2) our patient was very focused on her FEV_1 that had not returned to baseline after treatment of her MSSA.

NTM is becoming more prevalent in patients with cystic fibrosis. This is most likely a consequence of patients living longer as well as increased detection as physicians are ordering AFB analyses more frequently. A recent large multicenter study found 13% of patients with CF culture NTM [2]. A subset of NTM is the rapidly growing mycobacteria, which includes *M. abscessus*, *M. fortuitum*, and *M. chelonae*. *M. abscessus* is the third most common NTM and accounts for 80% of all rapidly growing mycobacteria pulmonary disease.

Pathophysiology. The pathogenesis of NTM pulmonary disease is not well known; however, it is thought to have significant overlap with the pathogenesis of tuberculosis. NTM have been recovered from water, soil, animals, and food products. NTM pulmonary disease most likely occurs after inhalation of aerosols from water reservoirs.

Patients frequently present with cough and fatigue as well as fever, weight loss, dyspnea, and hemoptysis. In CF, these symptoms are frequently found in patients

with a pulmonary exacerbation due to their bacterial pathogens. Therefore, it reinforces the importance of treating other infections first to attempt to isolate the contribution of *M. abscessus* to pulmonary symptoms.

Imaging. Chest imaging reveals multilobar patchy infiltrates with a predilection for the upper lobes. On high resolution CT scans, small nodules or a tree-in-bud pattern can be appreciated. Approximately, 1/6 patients will have associated cavitary disease.

Treatment. With current therapeutic options for *M. abscessus* pulmonary disease, it is exceedingly rare to successfully achieve eradication. In fact, *M. abscessus* is frequently a persistent infection that requires intermittent treatment, similar to the experience with *Pseudomonas aeruginosa* in patients with CF. It is important to stress this point with patients so that they do not become discouraged if *M. abscessus* is cultured during or after treatment. Since eradication will most likely not be achieved, the goals of therapy include improvement in symptoms and radiographic changes attributed to *M. abscessus* while suppressing the infection. To achieve these goals, combination therapy with oral, intravenous, and nebulized medications should be considered.

Guidelines recommend a total of 6–12 months of treatment [1]. Due to side effects and toxicities associated with *M. abscessus*, a full course of treatment may not be possible. Traditional antituberculosis medications do not have activity against *M. abscessus*, therefore antibacterial antibiotics are chosen. The first 1–2 months consist of combination treatment with (1) Amikacin and (2) cefoxitin or imipenem, and (3) clarithromycin or azithromycin. For the next 10–11 months of treatment, the patient should continue to receive an oral macrolide in conjunction with another agent, such as linezolid. The dosing of linezolid can be once daily (as opposed to the twice daily dosing for methicillin-resistant staphylococcus aureus) as this will minimize side effects and still provide antimycobacterial activity. At our center, we frequently have patients nebulize amikacin twice a day every other month. Side effects can be serious and are common in *M. abscessus* medications. These should be discussed in detail with patients prior to starting therapy [3]. Baseline audiometry and ophthalmology exams should be obtained. During therapy, patients can monitor red-green visual acuity at home using free tools on the internet. Frequent blood draws to monitor for blood dyscrasias, liver function, and renal function should also be performed.

After discussing all of the potential side effects and toxicities of therapy and the potential benefits with our patient, we decided to begin therapy. She was started on intravenous amikacin, intravenous cefoxitin, oral azithromycin, and oral linezolid. Four weeks after starting cefoxitin, she developed a fever. She went to a local emergency department and the workup revealed she was neutropenic. Neutropenia resolved with the discontinuation of the cefoxitin. We attempted to substitute tigecycline for cefoxitin; however, refractory nausea limited its use. At the conclusion of IV therapy, her FEV_1 was 97% (above her baseline) and she did not have any pulmonary symptoms. At this point, we added every other month nebulized amikacin twice a day to her regimen. She continues to tolerate her therapy without incident and during close follow-up has not subsequently cultured *M. abscessus*.

Case 2

Our patient is a 31-year-old man with cystic fibrosis with a baseline FEV_1 of 81% predicted. His CF is complicated by a history of allergic bronchopulmonary aspergillosis (ABPA), sinusitis, and CF-related diabetes. The patient presented to our institution for a second opinion regarding recurrent pulmonary exacerbations. In the last 12 months, he experienced five pulmonary exacerbations that were severe enough to require intravenous antibiotics. This was unusual since prior to this time he had not required intravenous antibiotics for his CF lung disease. He stated that he would feel better during treatment, but would relapse quickly after cessation of the antibiotics. Currently, he continues to complain of fevers, increasing dyspnea on exertion, cough, sputum production, and fatigue.

Review of systems. He had not been experiencing arthralgias, rashes, or other localizing symptoms and denied infectious exposures or overseas travel.

Physical examination. He appeared as a pleasant, well nourished male in no acute distress. Vitals were normal with an oxygen saturation of 96% while breathing ambient air. HEENT: Normal. Heart: regular rhythm with no murmur. Chest: He was not barrel chested. No retractions or use of accessory muscles. Bilateral crackles in the upper lung fields. No wheezes. Abdomen: normal bowel sounds. No masses or organomegally. Extremities: 1+ clubbing, pink. The rest of the exam was within normal limits.

Diagnostic testing. His FEV_1 was 68% of predicted. Review of previous sputum cultures revealed pan-sensitive *Pseudomonas aeruginosa*. On the day of the clinic visit, we obtained a CT scan of the chest, which revealed a new right lower lobe infiltrate in addition to his chronic bilateral upper lobe bronchiectasis.

With Presented Data, What Is Your Working Diagnosis?

This is a 31-year-old male with CF with recurrent pulmonary exacerbations despite appropriate treatment of previously cultured organisms and a new infiltrate.

Differential diagnosis. See Table 16.2. The differential diagnosis for a CF exacerbation that does not respond to treatment includes ABPA, pneumothorax, patent foramen ovale, CF-related diabetes, incorrect dosing of intravenous antibiotics, and emergence of resistance organisms such as *Burkolderia cepacia* complex or nontuberculosis *mycobacterium*.

Plan. We performed bronchoscopy with lavage of the infiltrate in the right lower lobe. Bronchoscopy is not routine in adult patients with CF because the risks of performing this invasive procedure are outweighed by the benefits of increased detection of pathogens. However, in situations where patients have symptoms despite treatment of pathogens identified on sputum culture, bronchoscopy may be helpful in detection of airway pathogens.

Table 16.2 Differential diagnosis for a CF exacerbation that does not respond to treatment

Diagnosis	Workup
Allergic bronchopulmonary aspergillosis	Serum total IgE, presence of anti-*Aspergillus* IgE antibodies, and/or serum precipitins or IgG antibody to *A. fumigates*
Cystic fibrosis-related diabetes	HgA_1C, oral glucose tolerance test, and/or 2 h post-prandial blood sugar
Pneumothorax	CT chest
Patent foramen ovale	ECHO with agitated saline contrast
Dosing of antibiotics	CF patients have accelerated renal clearance of antibiotics. Consult CF guidelines.
Emergence of resistant organisms	Bacterial, fungal, and mycobacterial cultures. Ask lab to hold CF specimens for several weeks.

Workup

The culture results from his bronchoalveolar lavage revealed a pan-sensitive strain of *Pseudomonas aeruginosa*. Fungal and mycobacterial smear and culture were negative. The total IgE level was normal and the hemoglobin A_1C was 6.0%. Review of his CT did not show a loculated pneumothorax.

The lab called 16 days later and stated the culture was growing *Nocardia farcinica*.

What Is Your Diagnosis and Why?

ABPA. He did have a history of ABPA, but his IgE level was normal and he did not have any wheezing.

Loculated pneumothorax. A review of his CT chest did not reveal a pneumothorax.

Patent foramen ovale. ECHO not ordered due to low probability in this patient.

CF-related diabetes. He had a history of diabetes and it was well controlled.

Incorrect dosing. We reviewed his outside records and he had received the recommended doses of intravenous aminoglycosides in patients with CF.

Emergence of resistant organisms. His strain of *Pseudomonas* was unchanged and he did not culture out a new fungal or mycobacterial organism. A review of the literature at that time stated that *Nocardia* was thought to be primarily a colonizer in patients with bronchiectasis, but due to his infiltrate on CT, decreased FEV_1, and recurrent symptoms with cessation of antibiotics, the most likely diagnosis was recurrent exacerbations due to *Nocardia farcinica*. Further bolstering the case for this being a pathogen as opposed to a colonizer is the patient had previously received prolonged courses of prednisone for his ABPA. Glucocorticoid therapy is one of the most common predisposing risk factors for *Nocardia*.

First-line therapy for *Nocardia* includes trimethoprim/sulfamethoxazole; however, the patient had an allergy so he was started on intravenous amikacin and a fluoroquinolone. After 6 weeks of combination therapy, he was continued on just an oral

fluoroquinolone for 1 year. Within a couple weeks of treatment, his fevers and sputum had resolved and his energy level and dyspnea had improved. A repeat CT of the thorax showed resolution of the RLL infiltrate. Several months after treatment for *Nocardia* had concluded, the patient developed bronchospasm and his IgE level was elevated. Due to the history of *Nocardia* infection, corticosteroids for ABPA were avoided and he was started on itraconazole. In order to evaluate if *Nocardia* had recurred, a repeat bronchoscopy was performed. The culture from the bronchoalveolar lavage only revealed his chronic strain of *Pseudomonas aeruginosa*.

Discussion

One common challenge in cystic fibrosis care is evaluating individuals with recurrent exacerbations despite frequent use of intravenous antibiotics. In this case, a difficult to diagnose infection was the etiology of recurrent exacerbations.

Nocardia is a ubiquitous, weakly acid fast, gram-positive aerobic bacterium found in the water and soil [4]. *Nocardia* can become pathogenic in patients with antecedent lung damage or underlying immune deficiencies and results in significant morbidity and mortality if untreated. In addition, there is a high relapse rate if not appropriately treated. While there are more than 50 species of *Nocardia*, *N. farcinica* is considered the most virulent. A high index of suspicion is critical as the diagnosis is challenging due to seldom encountering it in the cystic fibrosis population, a prolonged incubation period for culture, and an indolent clinical course mimicking granulomatous disease and malignancy.

Pathophysiology. Pulmonary infections due to *Nocardia* occur due to inhalation of the airborne organisms [5]. The importance of cell-mediated immunity in controlling infections is suggested by the association between *Nocardia and* immunosuppressed patients. Multiple mechanisms have been suggested to explain how *Nocardia* combats the immune system, including resistance to both phagocytosis and neutrophils.

The lungs are the most common site of infection due to *Nocardia*. The presentation can be acute, subacute, or chronic. Common symptoms overlap significantly with symptoms that any CF patient experiences and can include cough, sputum production, fatigue, decreased appetite with weight loss, and hemoptysis. Pulmonary *Nocardia* can result in contiguous spread to the pleura and mediastinum and hematogenous spread to the CNS, skin, and bone.

Workup. The diagnosis requires recovering *Nocardia* from a clinical specimen. *Nocardia* is notoriously difficult to culture and it usually requires an invasive procedure to make the diagnosis. Our case highlights this point as *Nocardia* was not recovered from repeated expectorated sputum samples over a 12-month period and was only diagnosed after bronchoalveolar lavage was performed. If the diagnosis is suspected, then the lab must be asked to hold the specimens several weeks beyond their usual monitoring period as *Nocardia* can have an incubation period from several days to several weeks. Finally, speciation of *Nocardia* can be difficult.

Identification of species is important because it impacts prognosis and treatment. For example, *N. farcinica* is considered the most virulent of the species and is resistant to multiple antibiotics. As *Nocardia* can spread to the brain, imaging of the CNS should be considered even in patients without neurologic symptoms.

Imaging studies. As with the clinical symptoms of *Nocardia*, imaging patterns are nonspecific and span a wide spectrum. They can include lobar consolidation (as seen in our patient), reticulo-nodular infiltrates, interstitial infiltrates, single or multiple nodules, and pleural effusions.

Treatment. There are no randomized controlled trials to guide therapeutic decision-making in patients with pulmonary *Nocardia*. Therefore, decisions are based on antibiotic susceptibilities and expert opinion. In general, most recommendations include treatment with two or three susceptible antibiotics [6]. In patients with pulmonary *Nocardia*, a combination of intravenous amikacin and intravenous or oral trimethoprim/sulfamethoxazole should be considered. Since our patient was allergic to trimethoprim/sulfamethoxazole, he received an extended spectrum fluoroquinolone. Other antibiotic combinations should be decided in consultation with an infectious disease expert. After 4–8 weeks of treatment with both antibiotics, the intravenous antibiotics can be discontinued and patients may be managed with a single oral antibiotic for the next 6–12 months. Long-term suppressive therapy should be considered in patients with irreversible risk factors.

Summary and Conclusions

Nocardia is an important pathogen in patients with cystic fibrosis. In CF patients with pulmonary exacerbations not responding to usual care, especially those who frequently relapse and have previously received glucocorticoids, *Nocardia* should be added to the differential. The microbiology lab should be informed to hold cultures for several weeks. If this pathogen is identified, it is critical for clinicians to administer the proper type and duration of therapy as undertreated *Nocardia* results in significant morbidity and mortality.

Questions

Case 1

1. The diagnosis of NTM lung disease requires which of the following:
   (a) Pulmonary symptoms
   (b) The exclusion of other diagnoses
   (c) At least two expectorated sputum samples
   (d) All of the above

2. Which of the following is true about treatment of NTM?

   (a) Treatments for NTM are well tolerated
   (b) The diagnosis of NTM does not necessarily imply immediate treatment
   (c) At least one antituberculosis medication should be included
   (d) *M. abscessus* is frequently eradicated from the respiratory tract of CF patients

3. What is the prevalence of NTM in the CF population?

   (a) 1%
   (b) 5%
   (c) 15%
   (d) 25%

4. Which one of the following is not a rapid grower?

   (a) *M. avium* Complex
   (b) *M. fortuitum*
   (c) *M. chelonae*
   (d) *M. abscessus*

5. NTM guidelines do not include which of the following antibiotics?

   (a) Cefoxitin
   (b) Amikacin
   (c) Ethambutol
   (d) Azithromycin

Case 2

6. Which one of the following is true about *Nocardia*?

   (a) Primarily found in skin of animals
   (b) Gram-negative rod
   (c) Acid fast
   (d) All of the above

7. What is the incubation period of *Nocardia*?

   (a) Several hours
   (b) One day
   (c) 1–3 days
   (d) Several days to several weeks

8. Which aminoglycoside is preferred in patients with *Nocardia*?

   (a) Tobramycin
   (b) Amikacin

(c) Gentamicin
(d) Kanamycin

9. What is the usual length of treatment of pulmonary Nocardia?

(a) 14 days
(b) 4–8 weeks
(c) 3 months
(d) 6–12 months

10. Which of the following is true about *N. farcinica*?

(a) It is considered the most virulent species of *Nocardia*
(b) It usually colonizes the respiratory tract of patients with cystic fibrosis
(c) It is usually sensitive to all antibiotics
(d) All of the above

Answer key: 1. (d), 2. (b), 3. (c), 4. (a), 5. (c), 6. (c), 7. (d), 8. (b), 9. (d), 10. (a)

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